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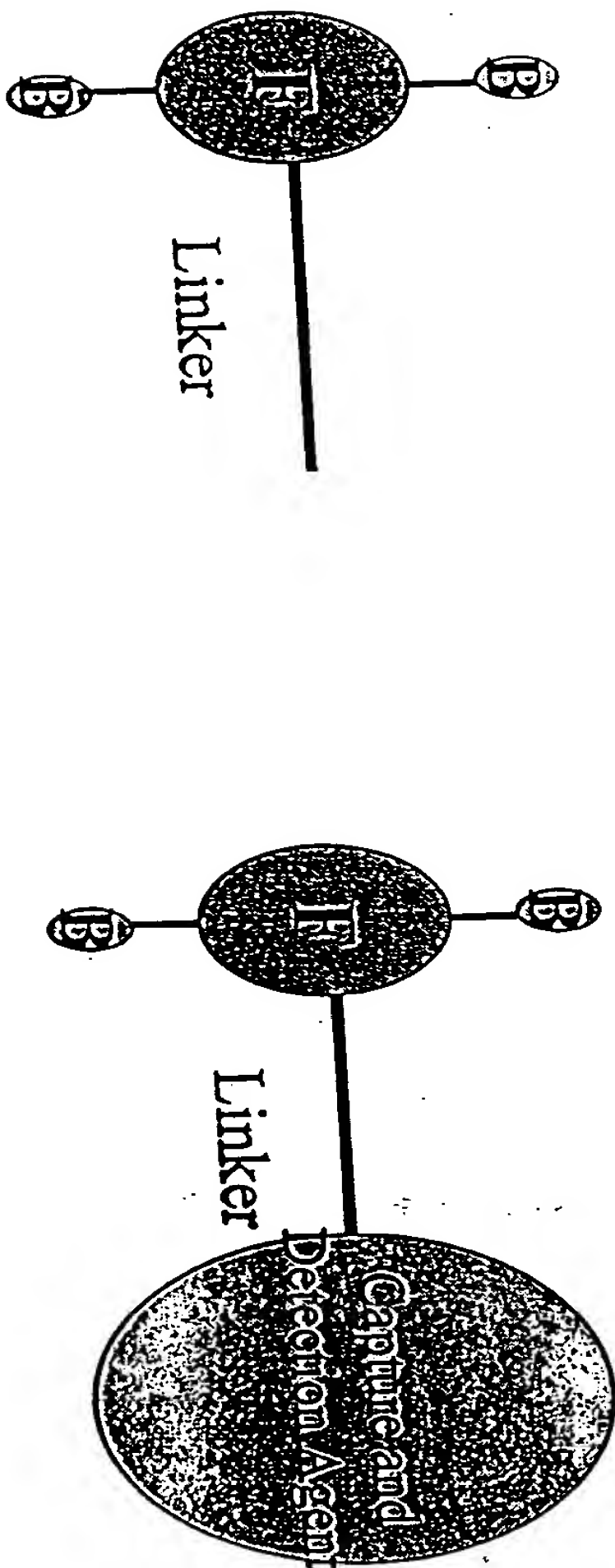
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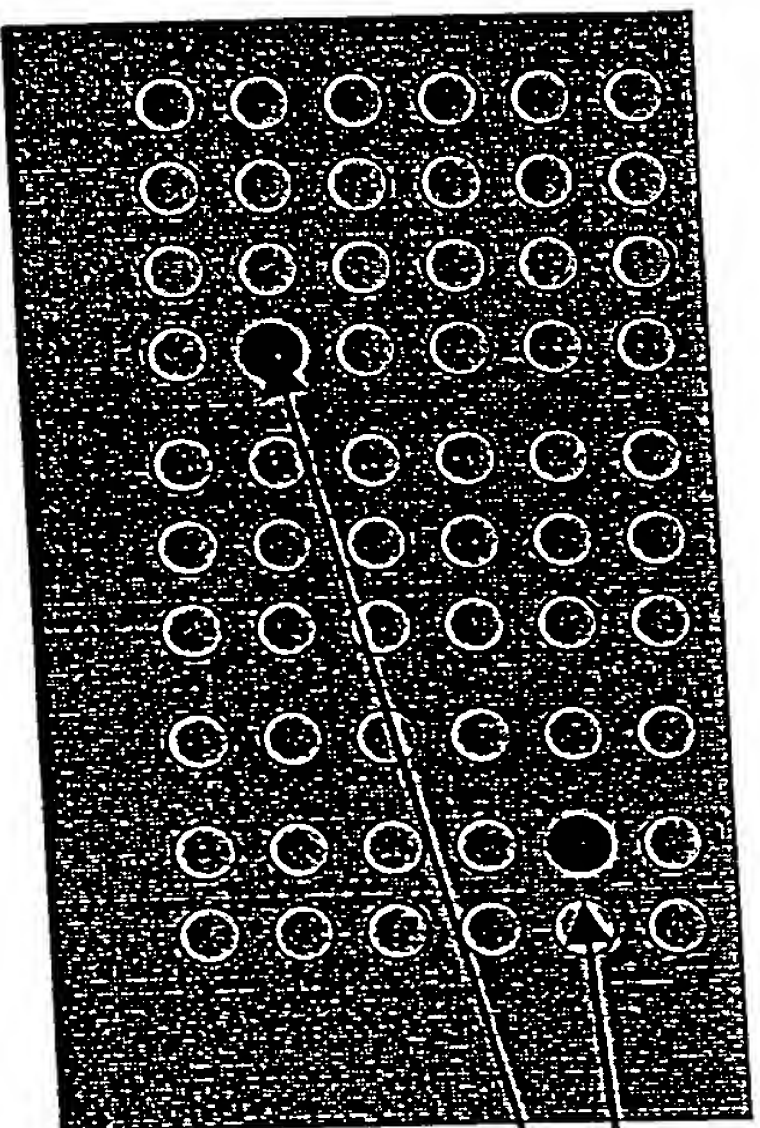
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High-throughput Target ID



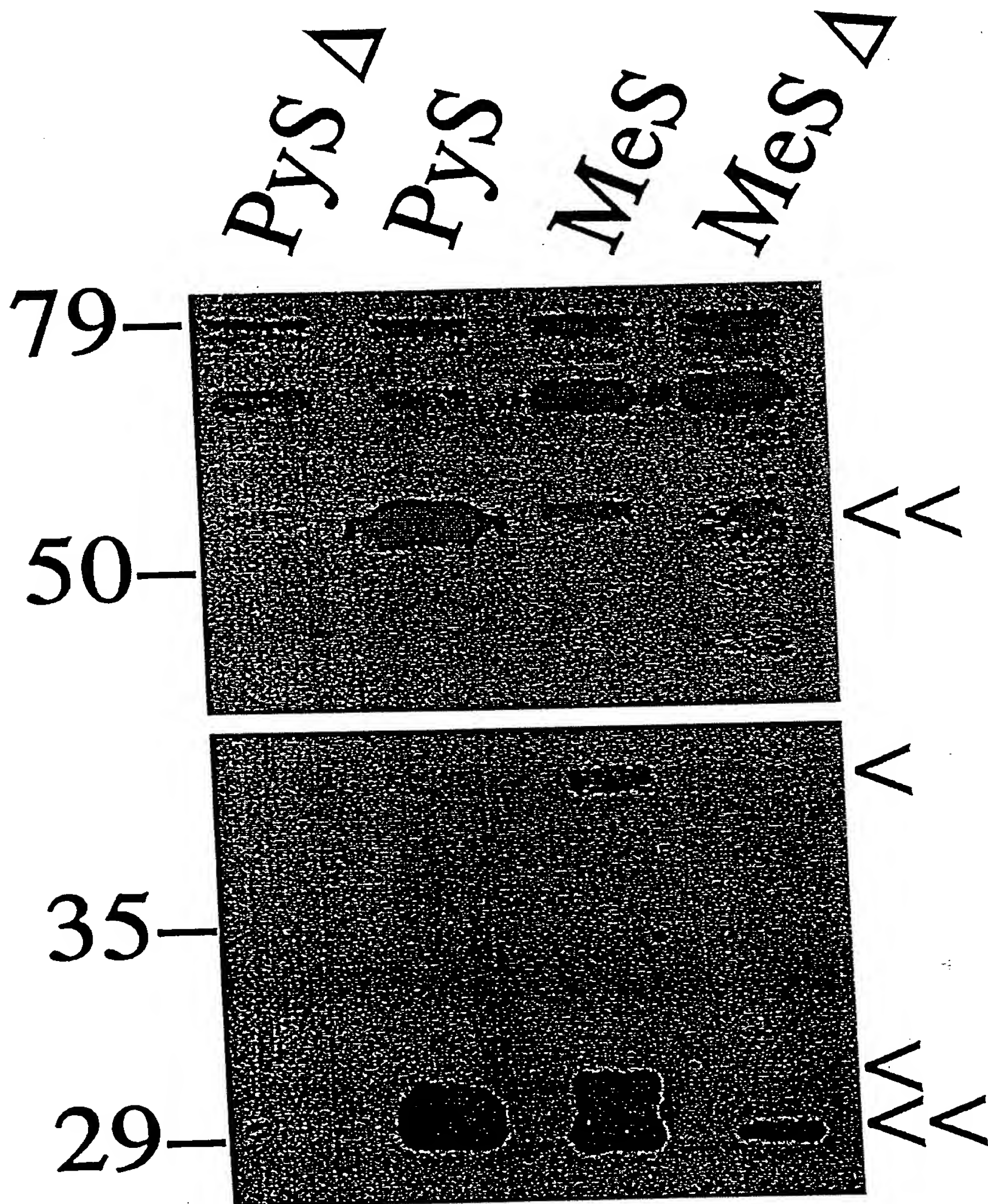
Library of Bioactive
Compounds

Library of Target ID
Compounds

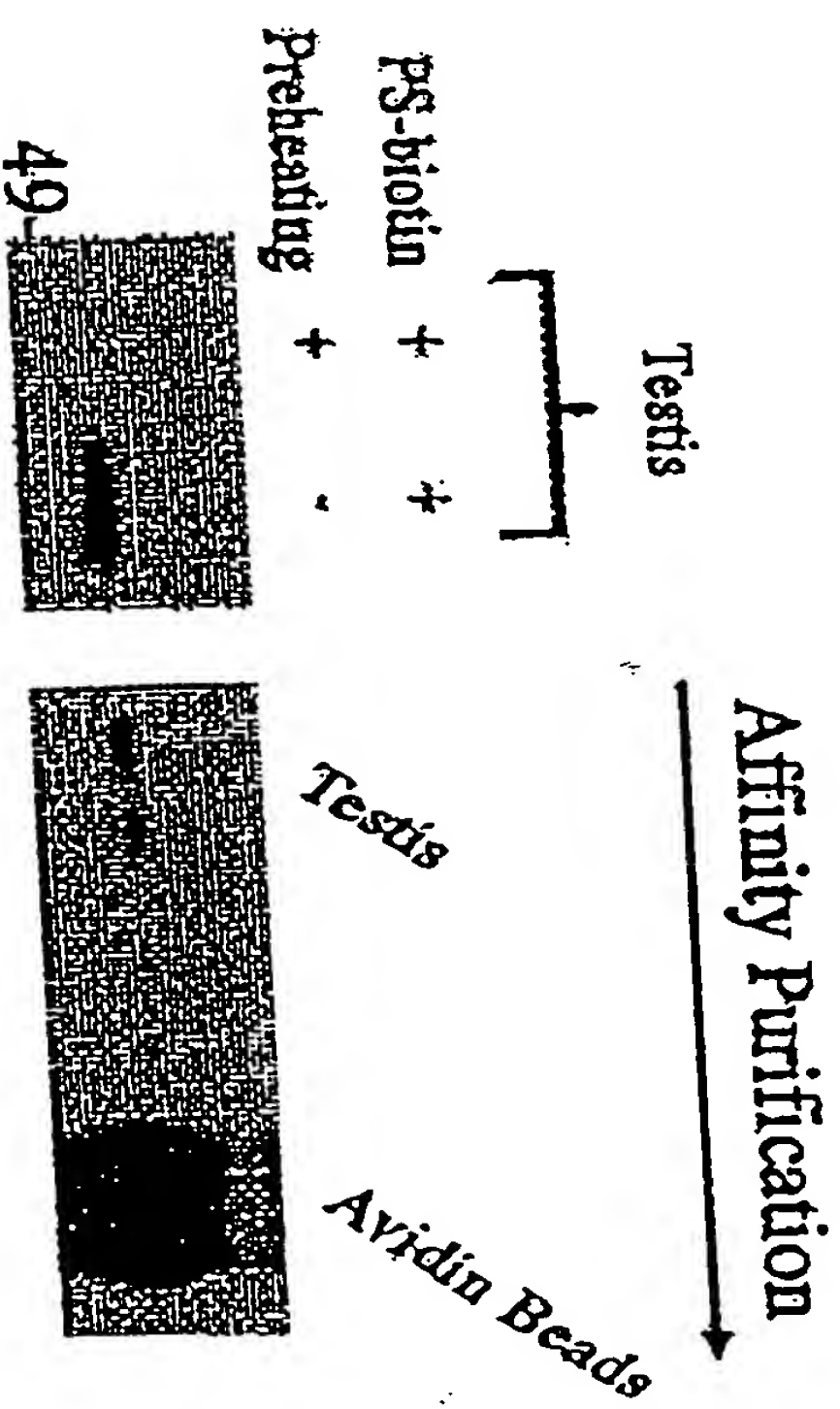
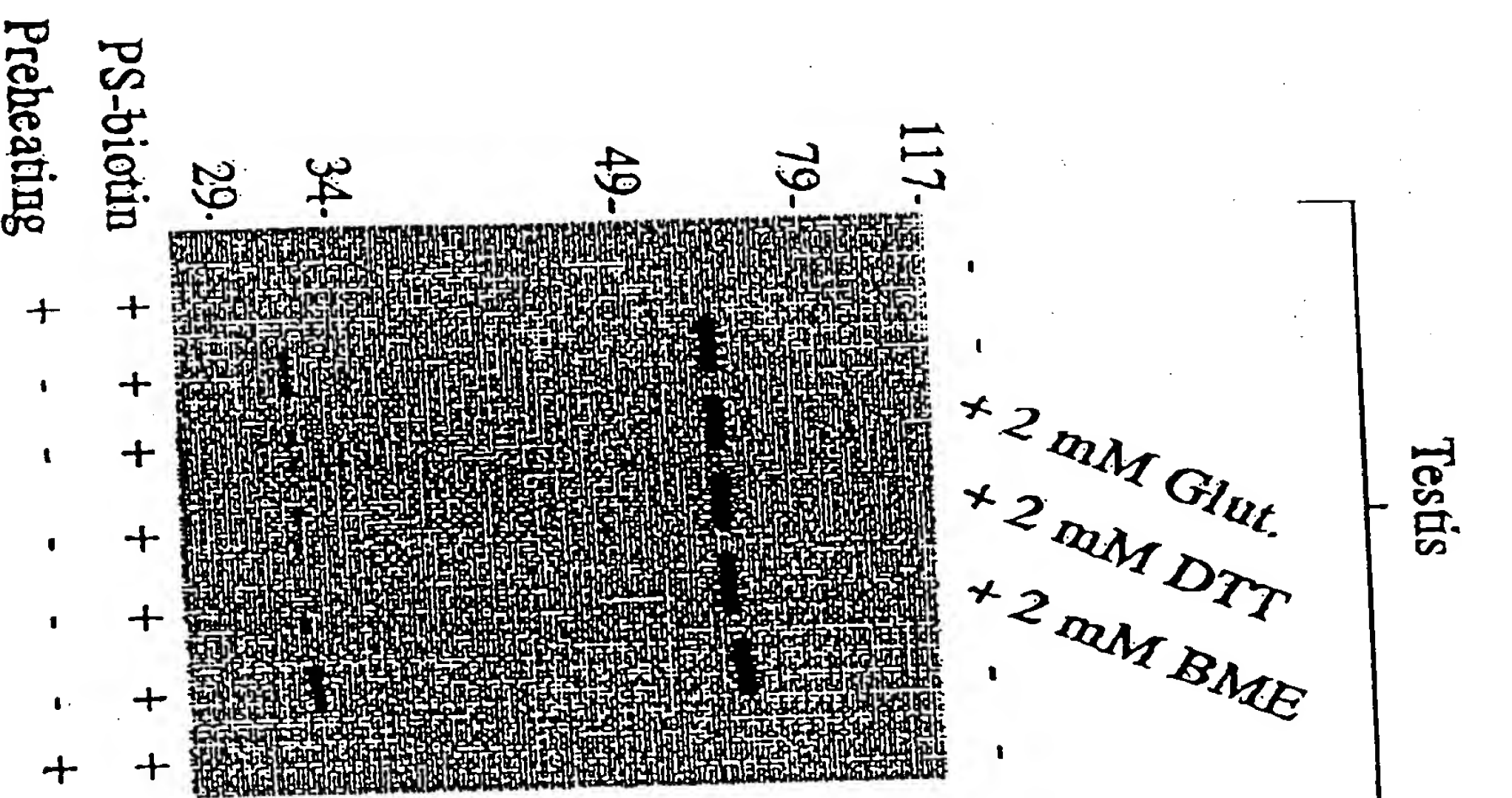


Use corresponding
activity-based probe to
identify the biological target

FIGURE 2



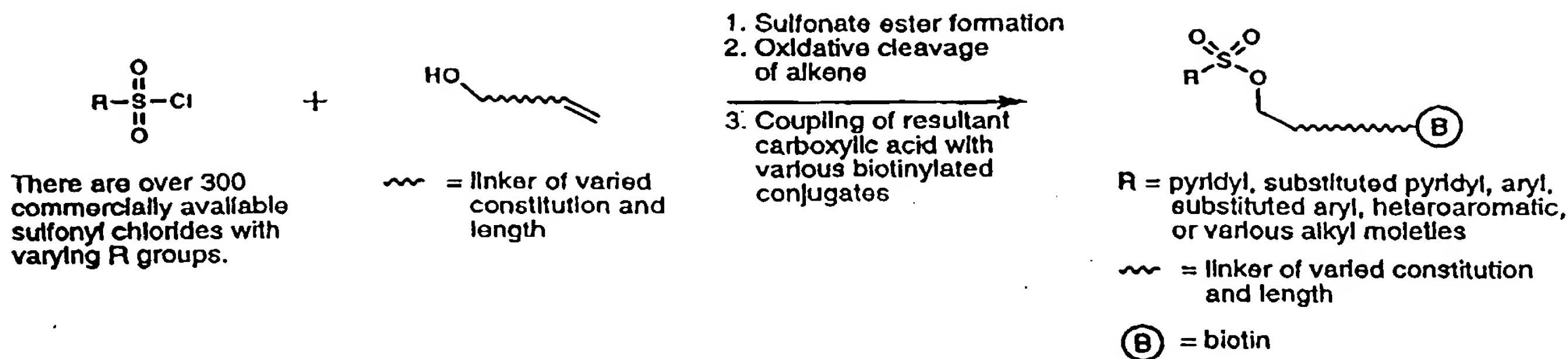
Non-Directed Tagged Library of Sulfonates Identifies Probe for ADH Superfamily of Enzymes



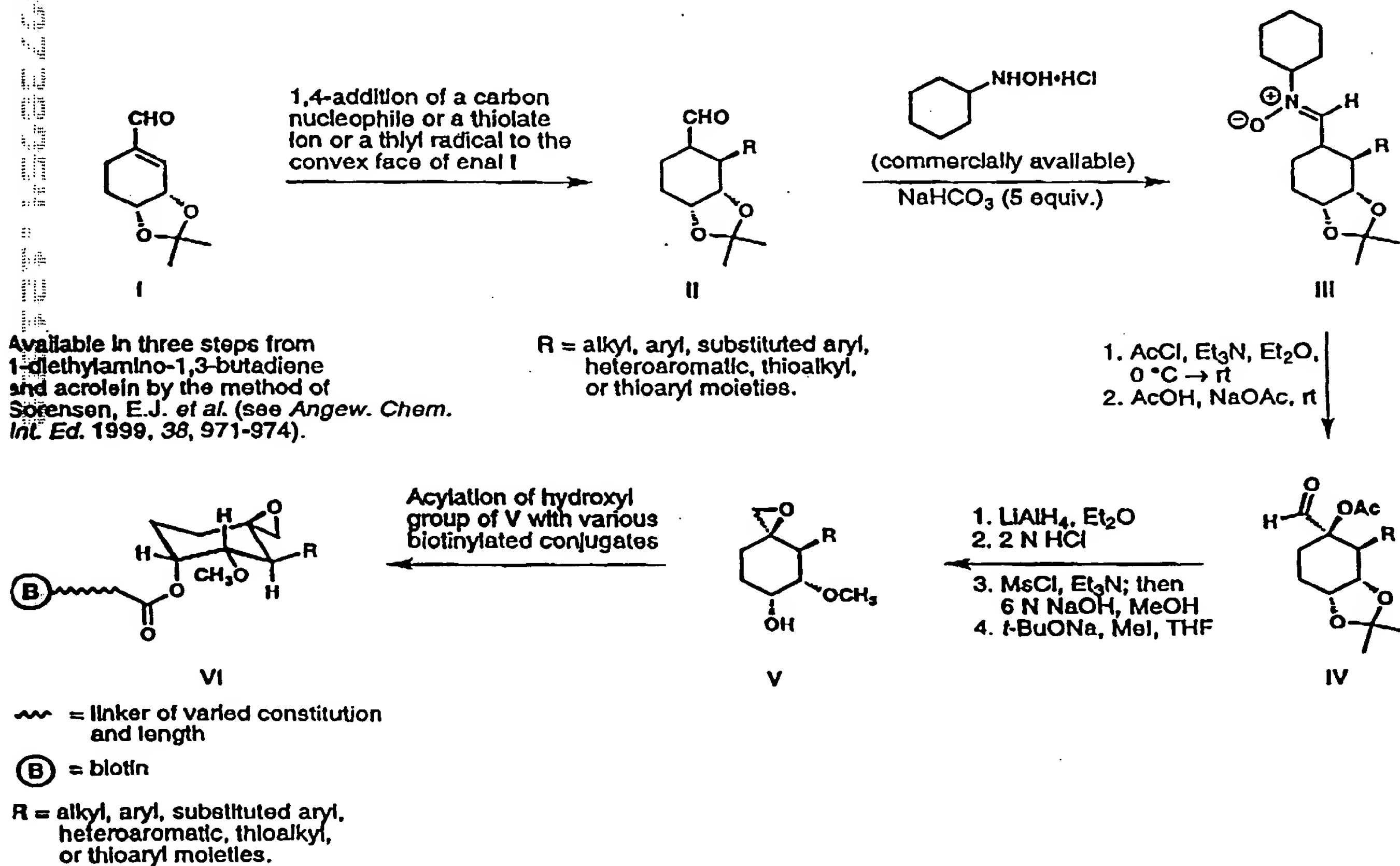
- MALDI mapping identifies tagged protein as aldehyde dehydrogenase (ADH, cytosolic class II)
- 28 ADHs in fly genome
 - Involved in retinoic acid biosynthesis and catabolism of alcohol and chemotherapeutic agents

FIGURE 3

FIGURE 4



Scheme 1. A pathway for syntheses of various biotinylated sulfonate esters for use in activity-based proteomics studies.



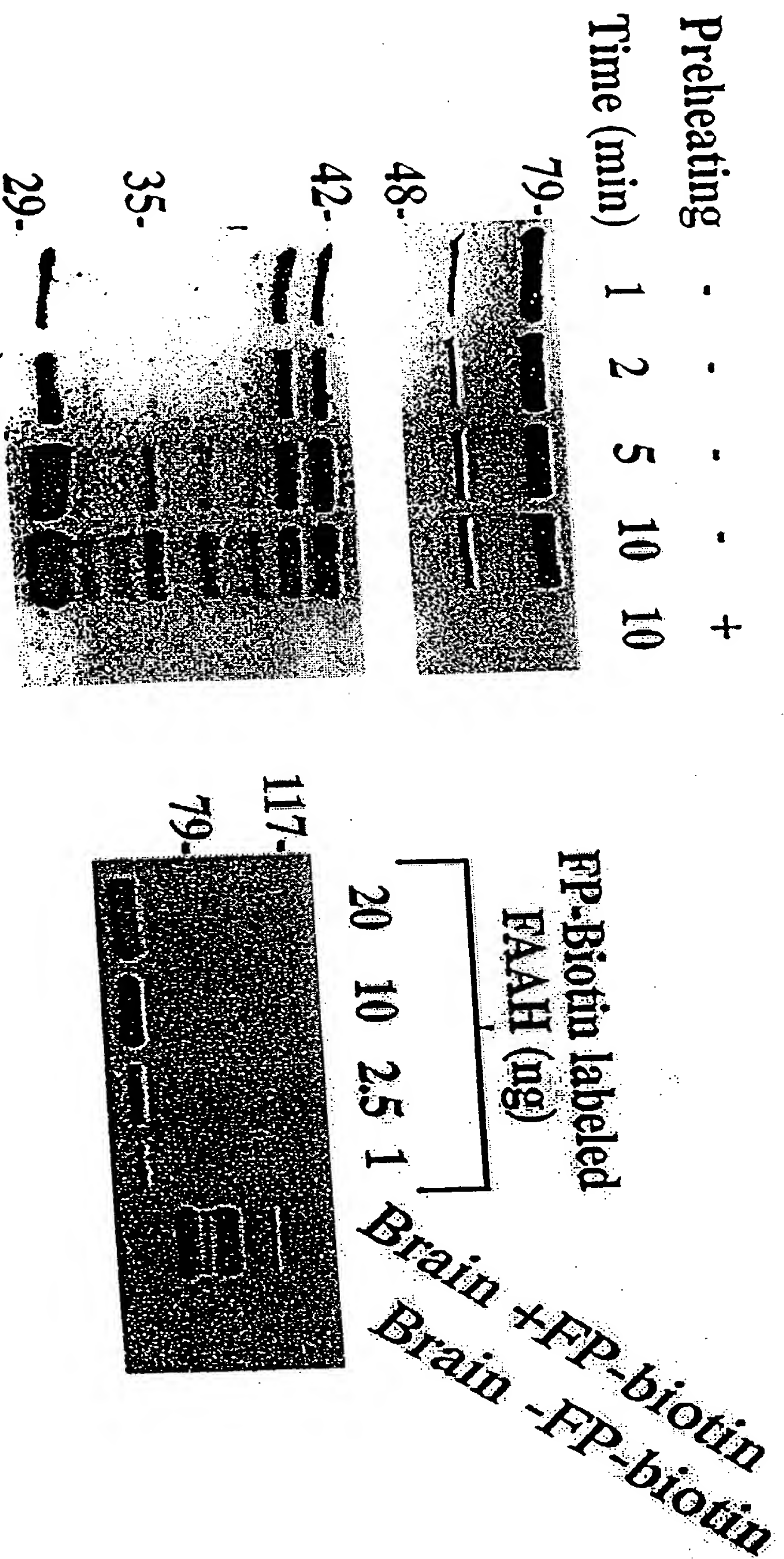
Scheme 2. A strategy for convergent, stereocontrolled syntheses of conformationally well-defined spiroepoxides of type VI. Literature precedent for $\text{I} \rightarrow \text{II} \rightarrow \text{III} \rightarrow \text{IV} \rightarrow \text{V}$ can be found in Sorensen, E.J. *et al.* *Angew. Chem. Int. Ed.* 1999, 38, 971-974. Compounds of type VI are analogs of the metalloprotease (MetAp-2) inhibitor fumagillin and will be employed as covalent affinity agents in activity-based proteomics studies.

FP-Biotin: a kinetic reporter of SH Activity

The rates at which the majority of SHs react with FP-biotin can be experimentally followed

FP-biotin readily detects low femtomole quantities of SHs directly in complex cell/tissue proteomes

FIGURE 5



Utility of Multiplexed probes in identifying Serine Hydrolases

FP-peg-biotin (μ M) 4 2 0 2
 FP-biotin (μ M) 0 2 4 2
 Preheated . . . +

Preheating + - - +
 FP-peg-biotin - - + +
 FP-biotin + + - -

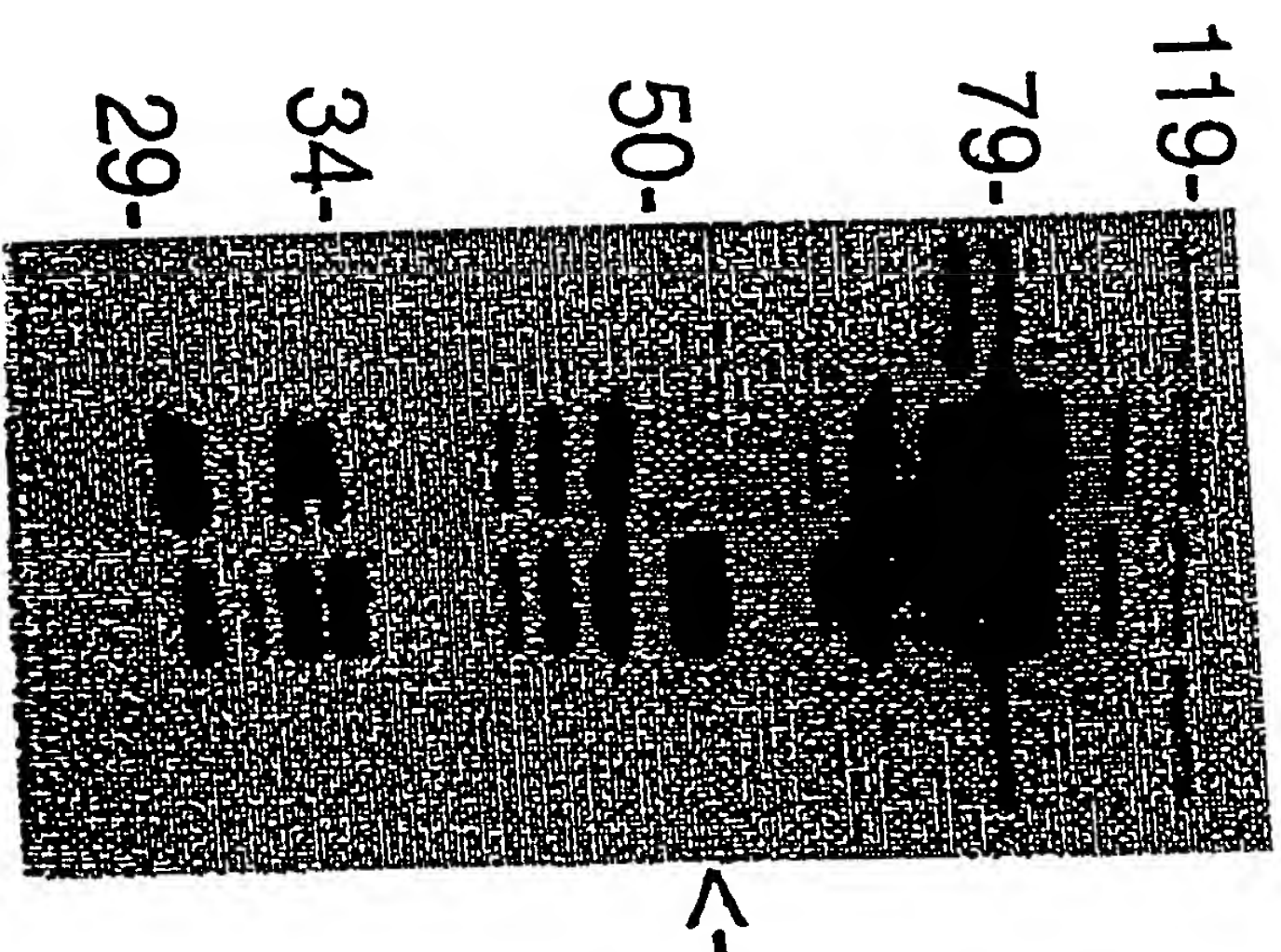
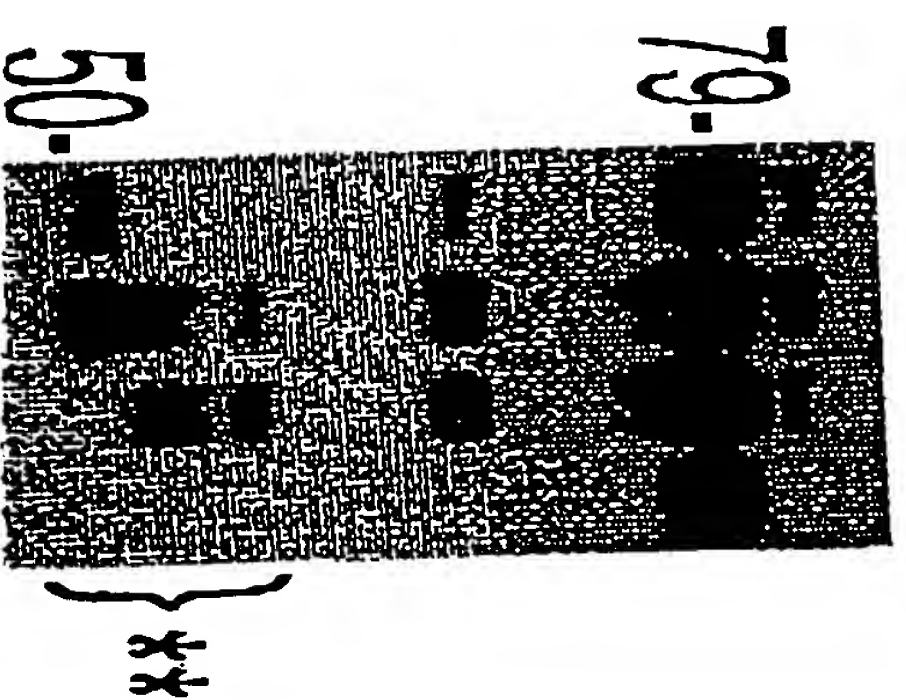
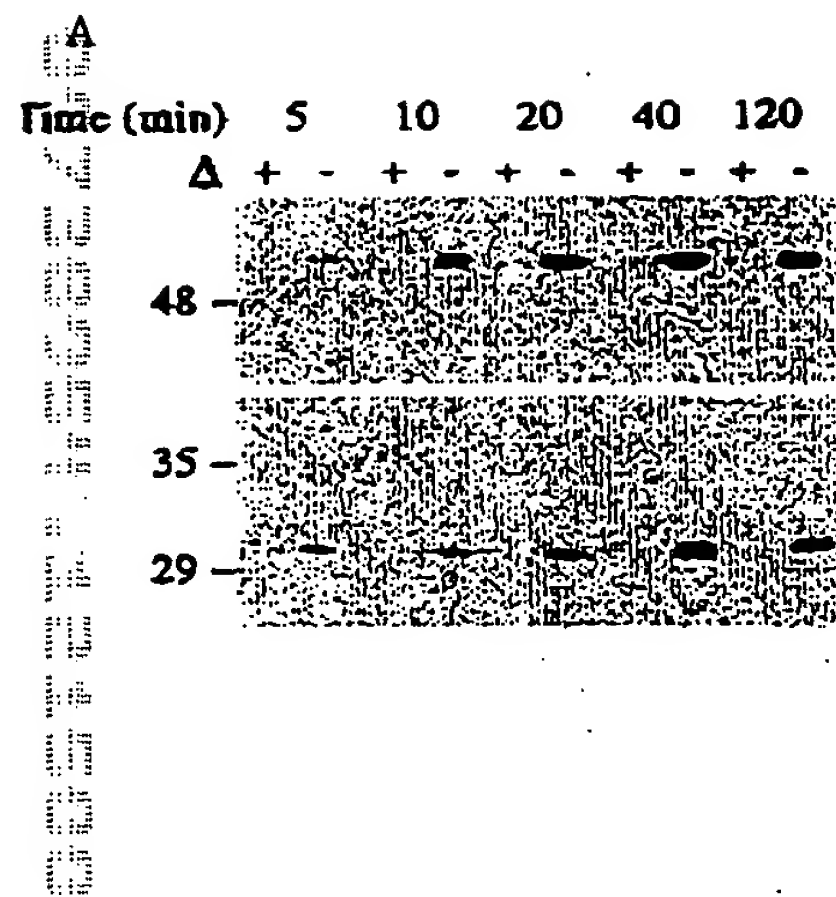


FIGURE 6

FIGURE 7



B

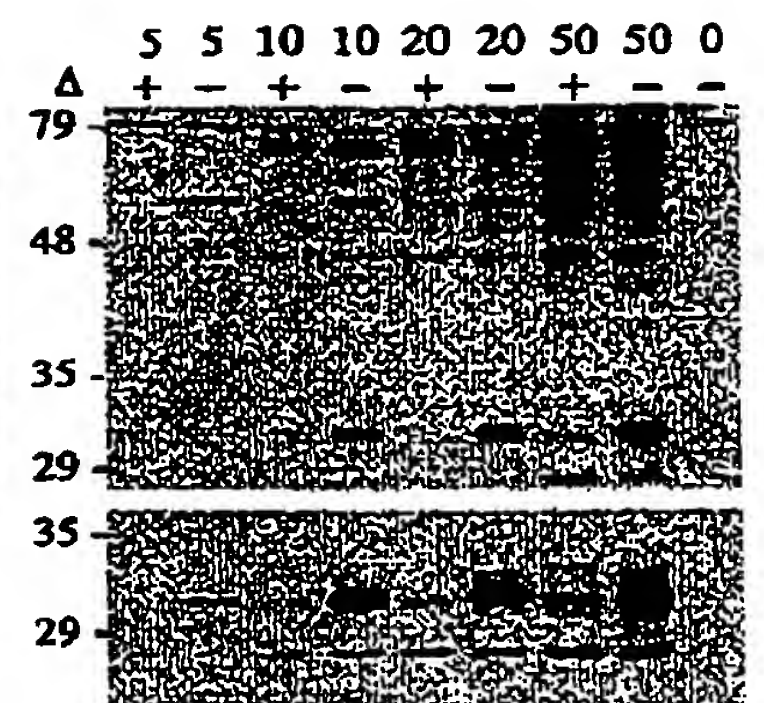
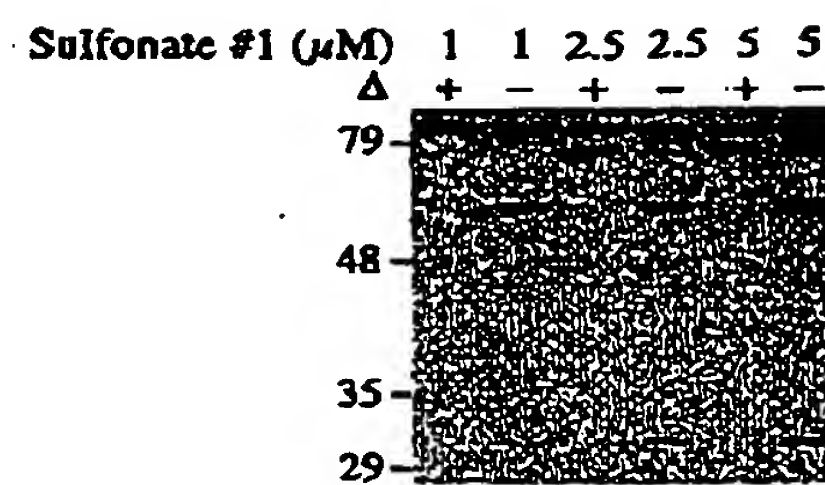
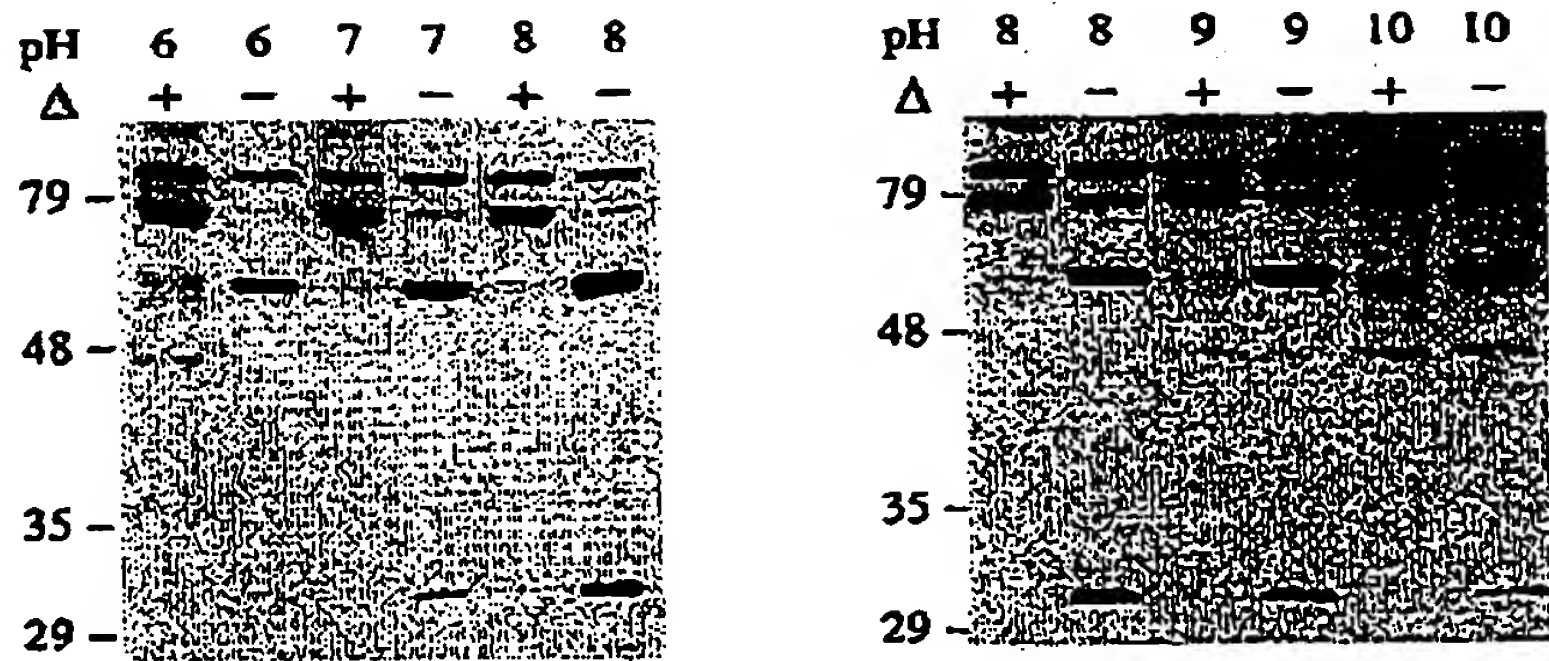


FIGURE 7

C



D

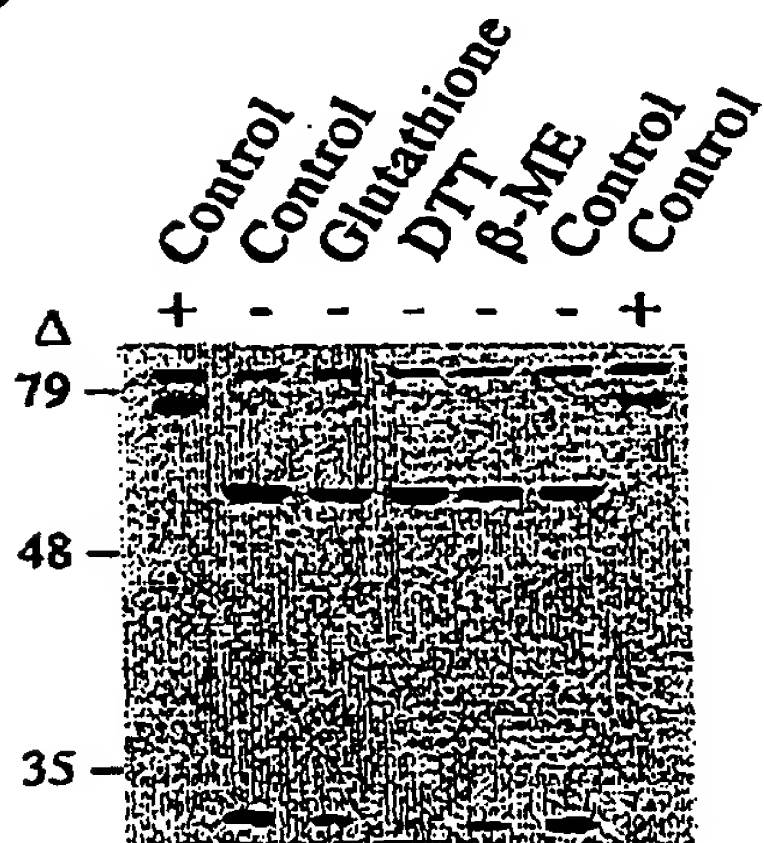


FIGURE 8

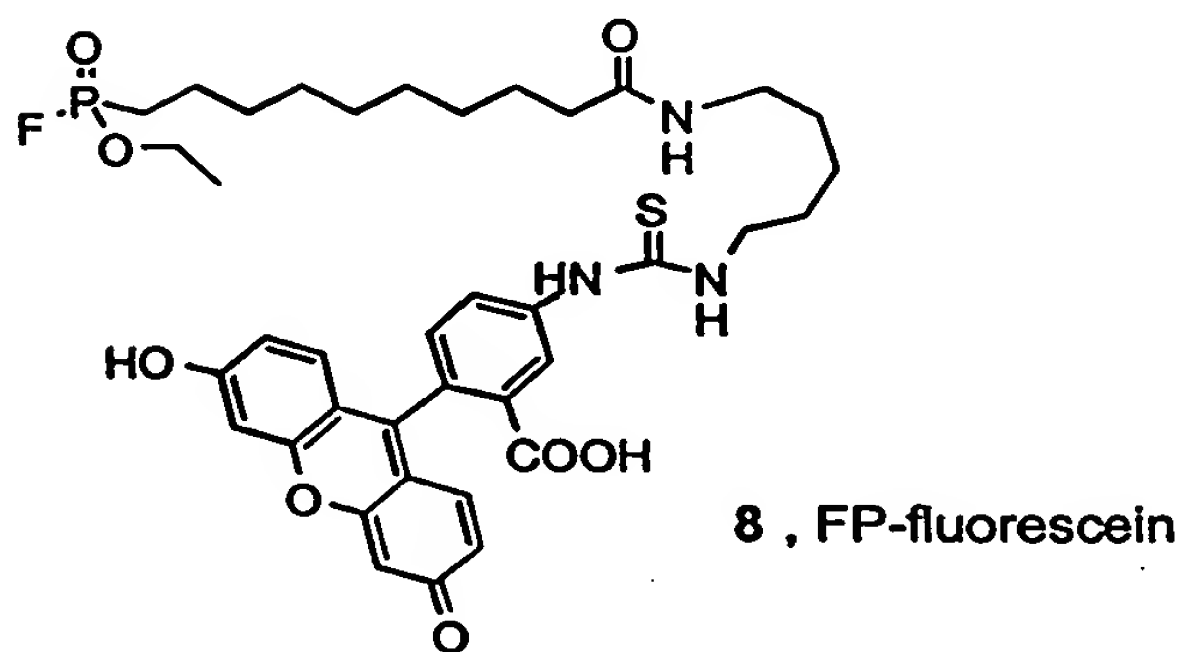
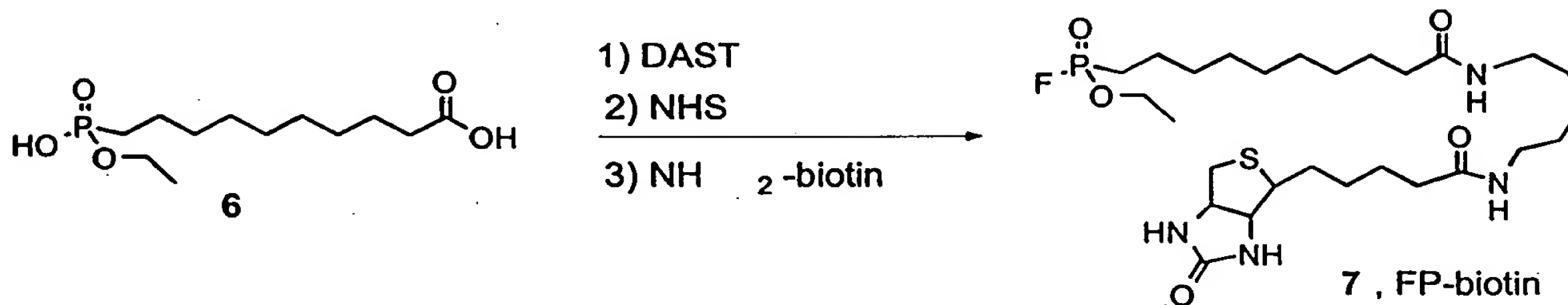
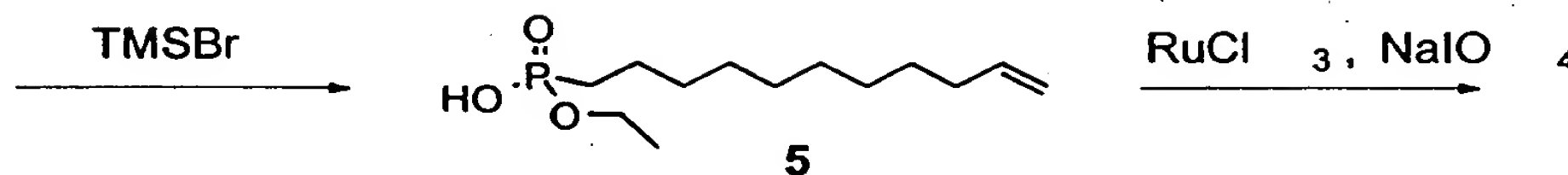
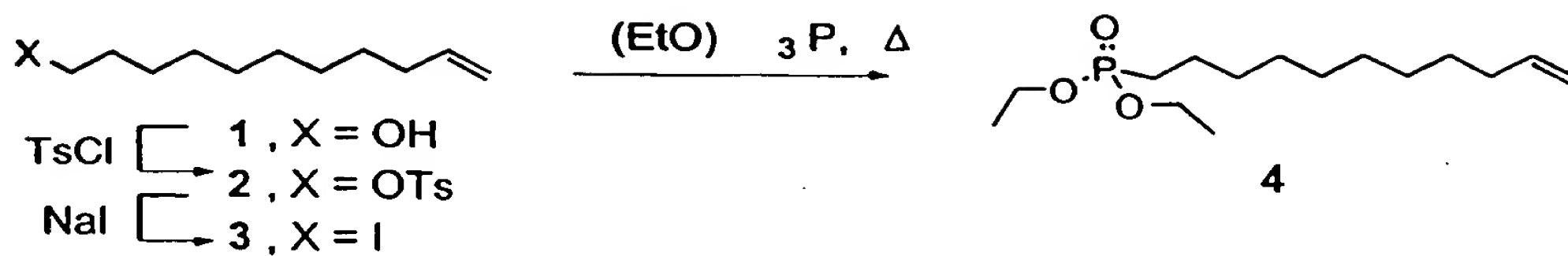
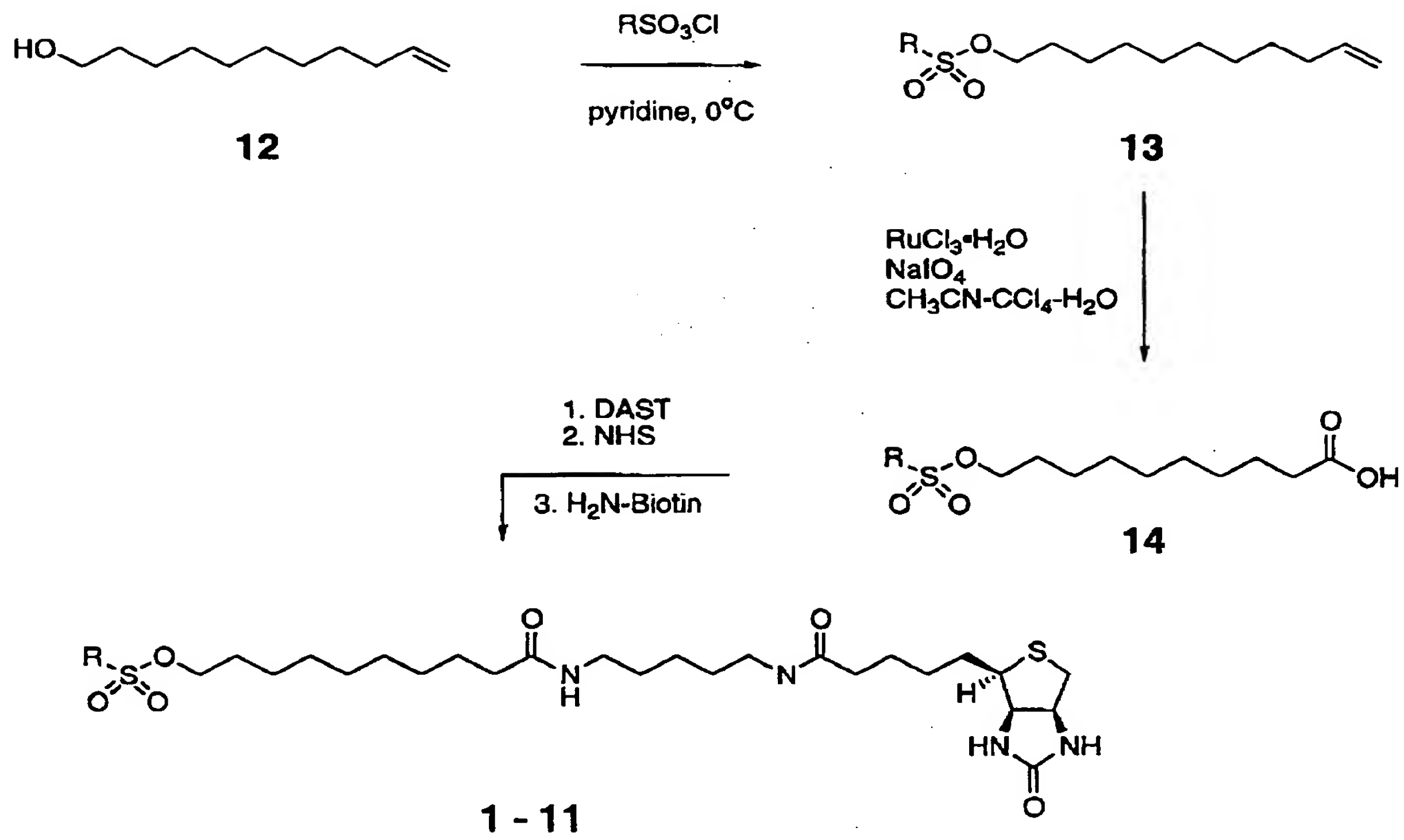
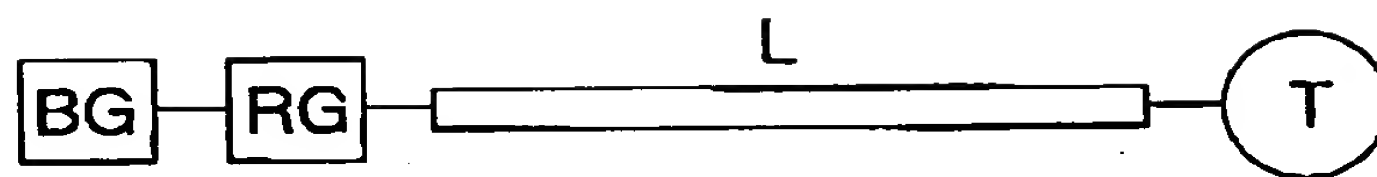


FIGURE 9



A.



B.

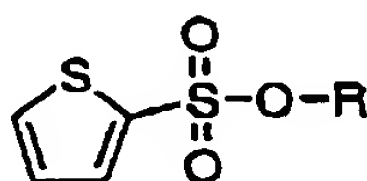
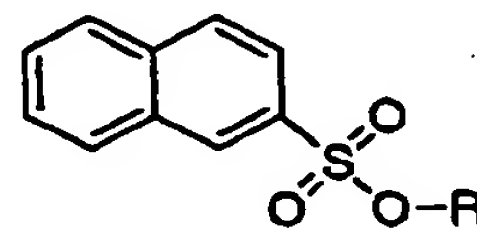
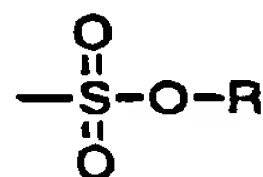
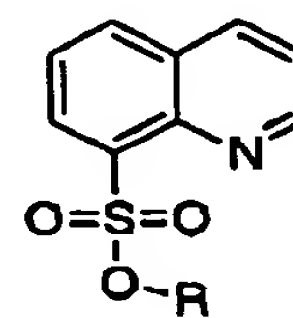
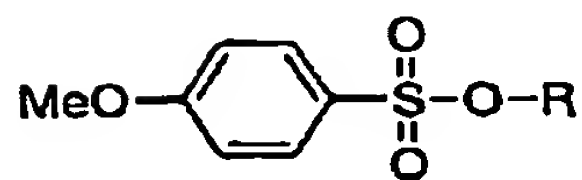
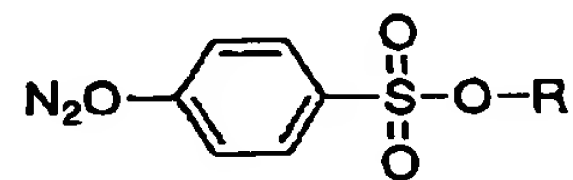
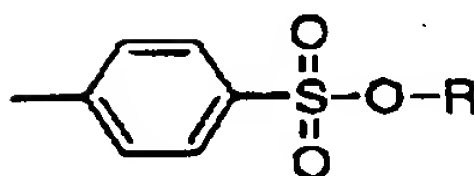
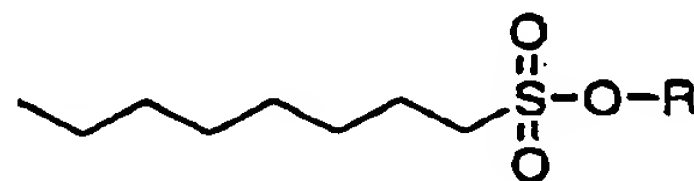
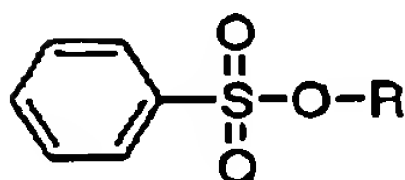
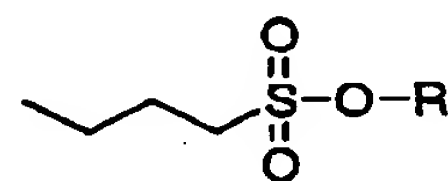
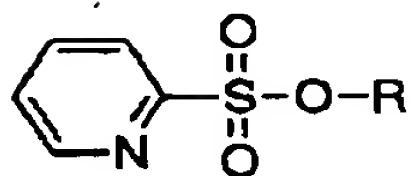
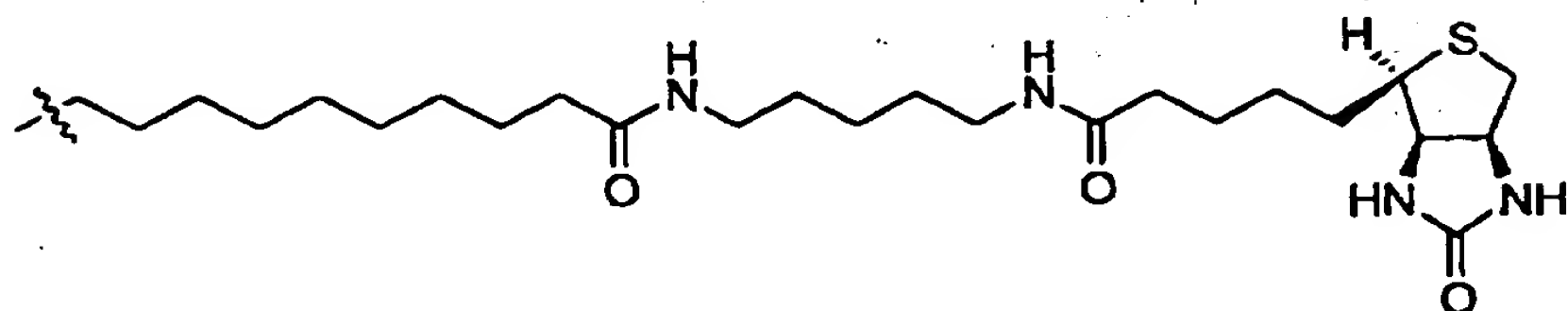
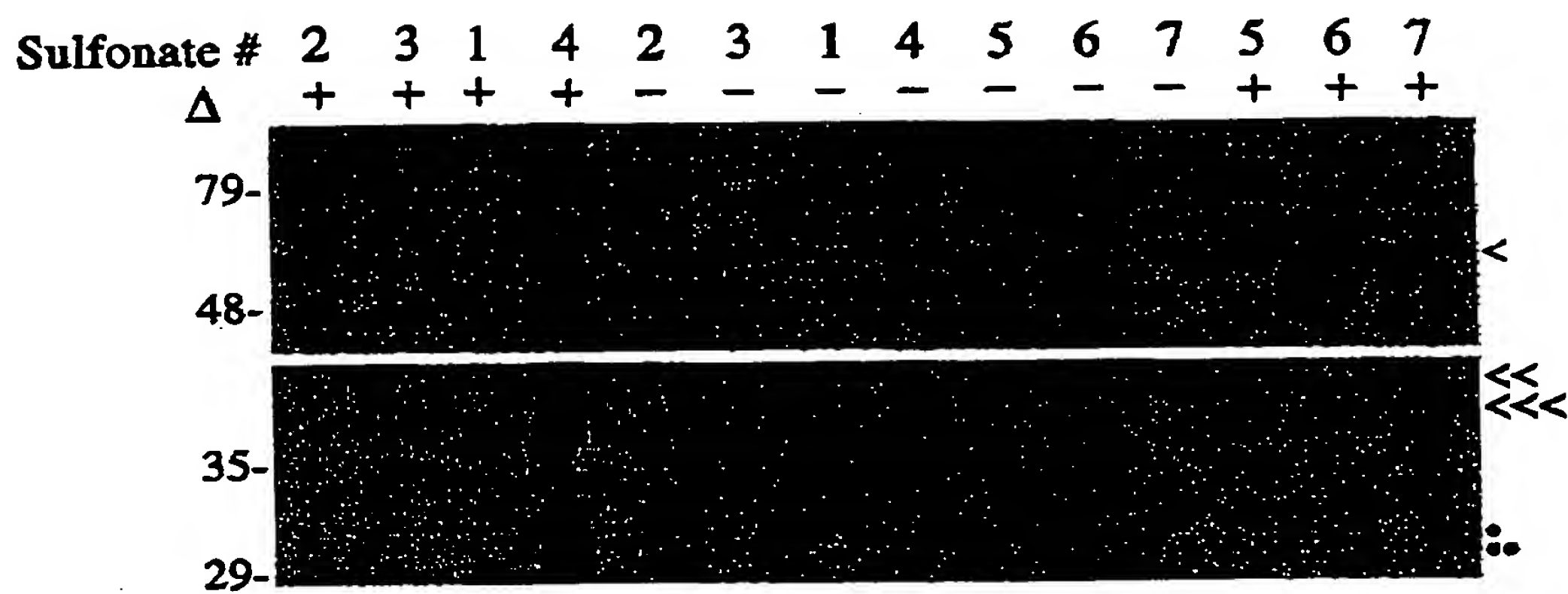


FIGURE 11

A



B

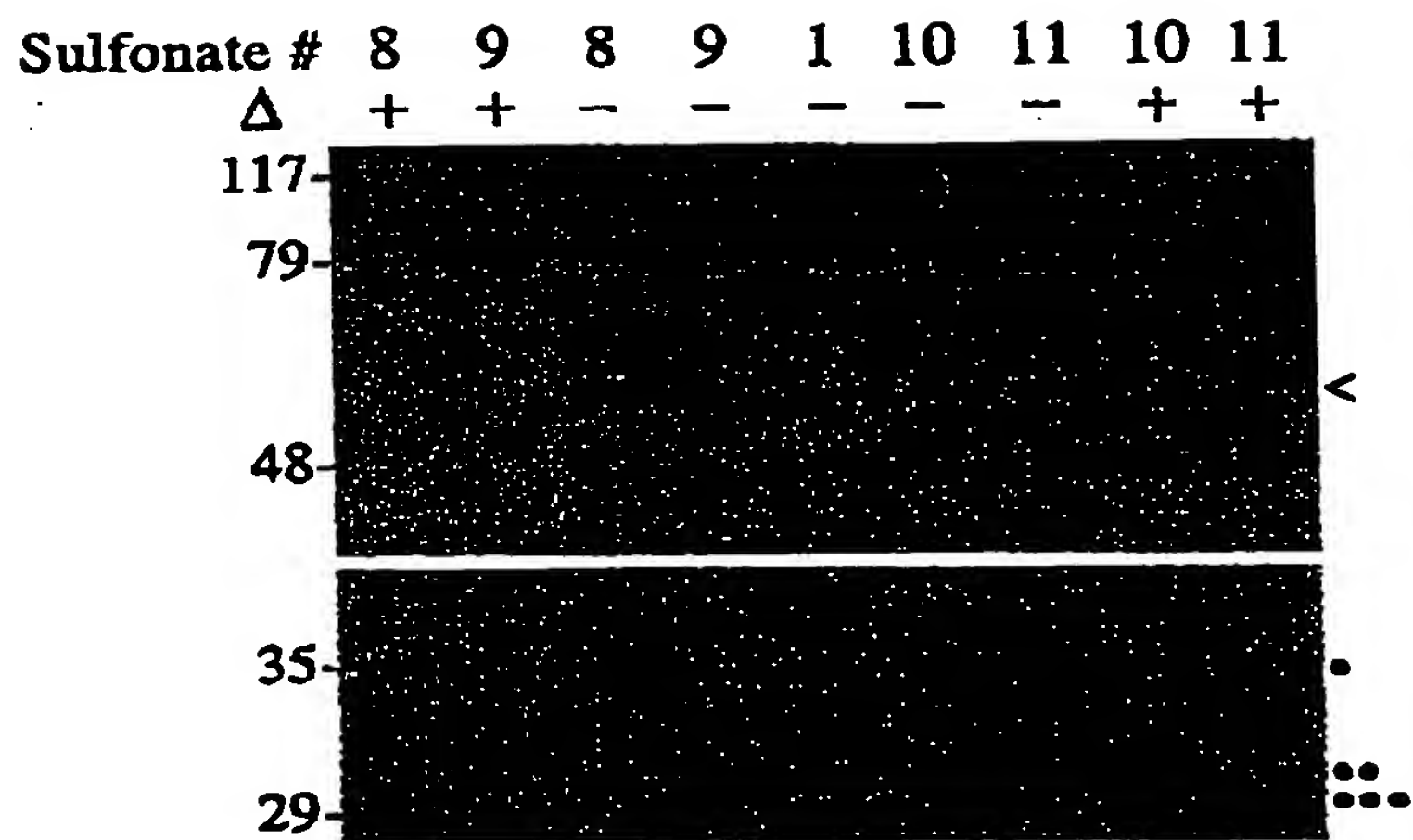
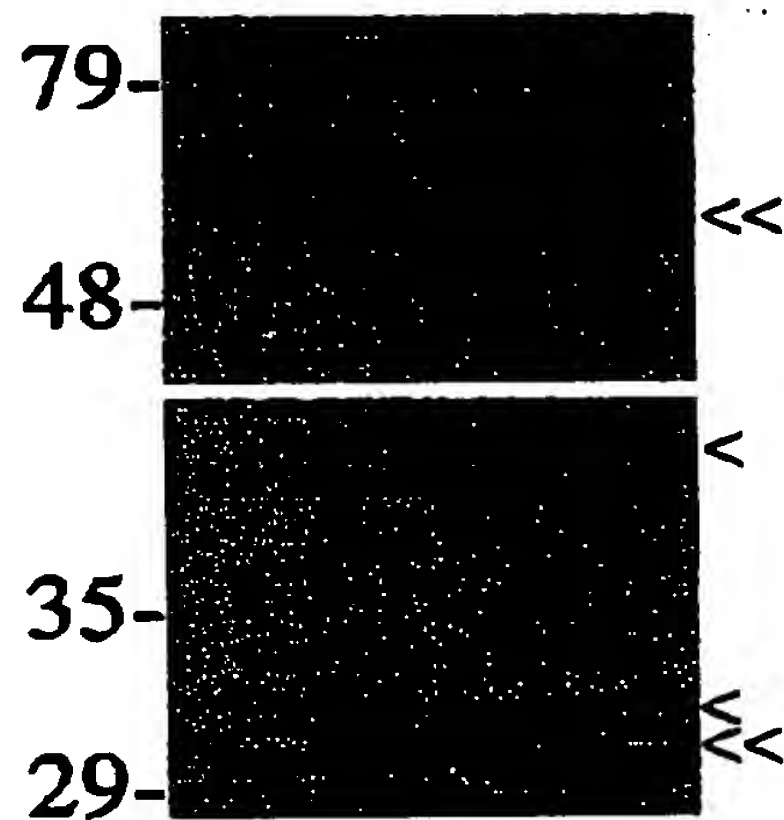


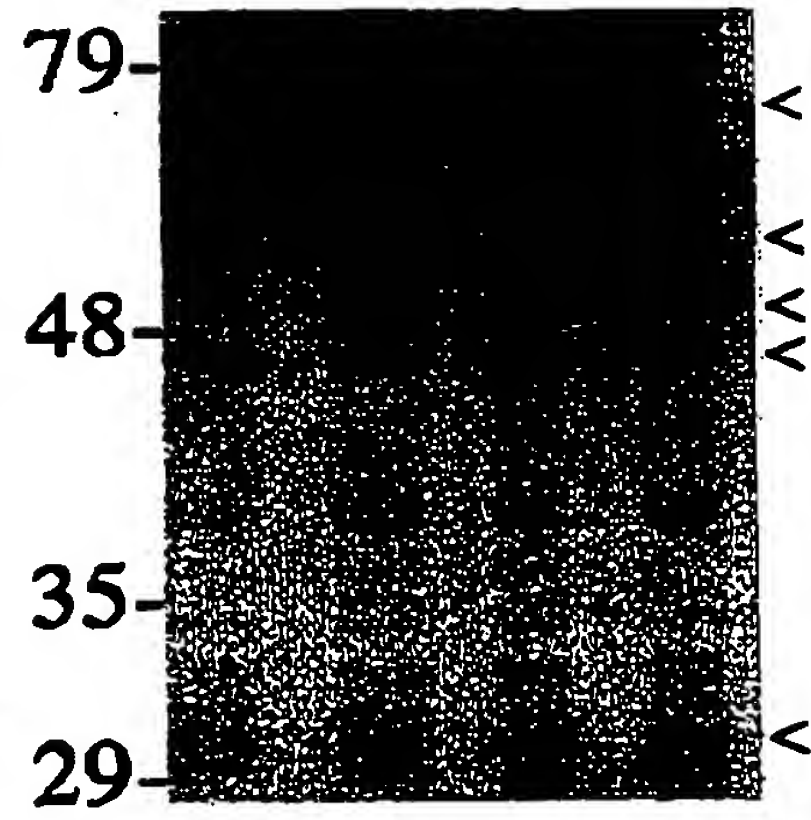
FIGURE 12

A

Sulfonate # 1 1 5 5
 Δ + - - +

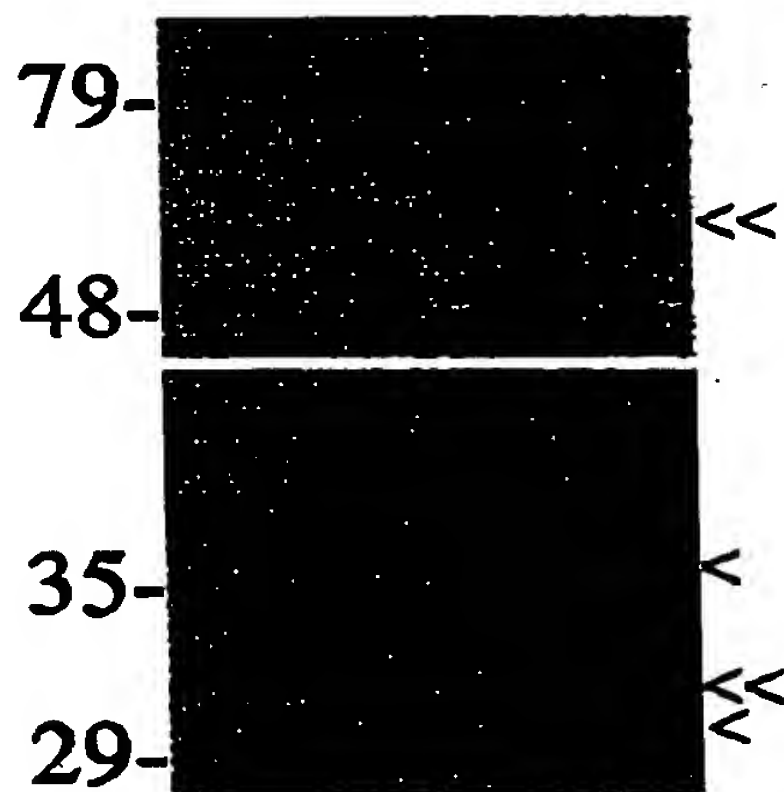


1 1 5 5
+ - - +



B

Sulfonate # 1 1 9 9
 Δ + - - +



1 1 9 9
+ - - +

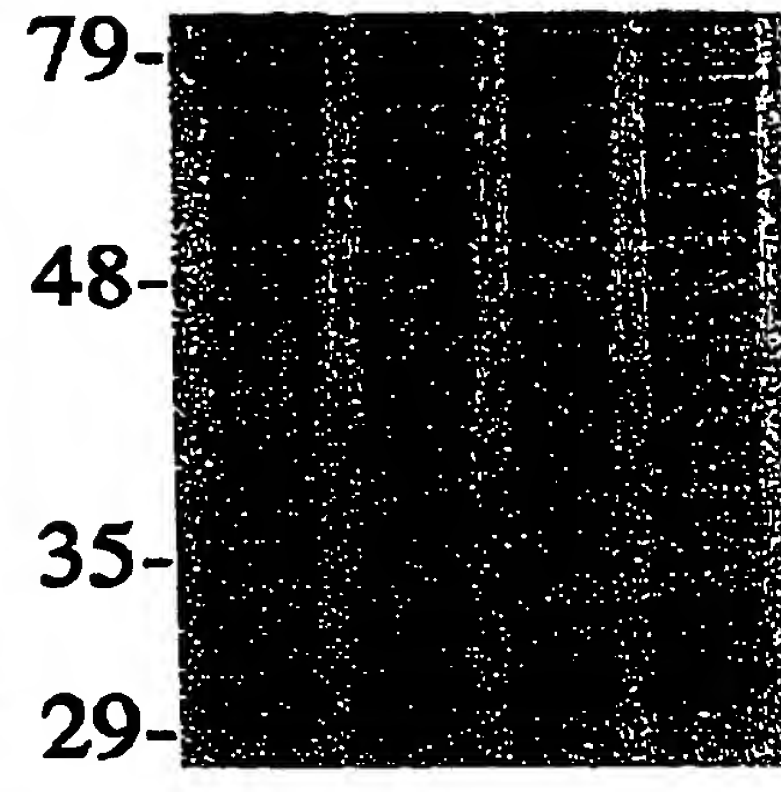
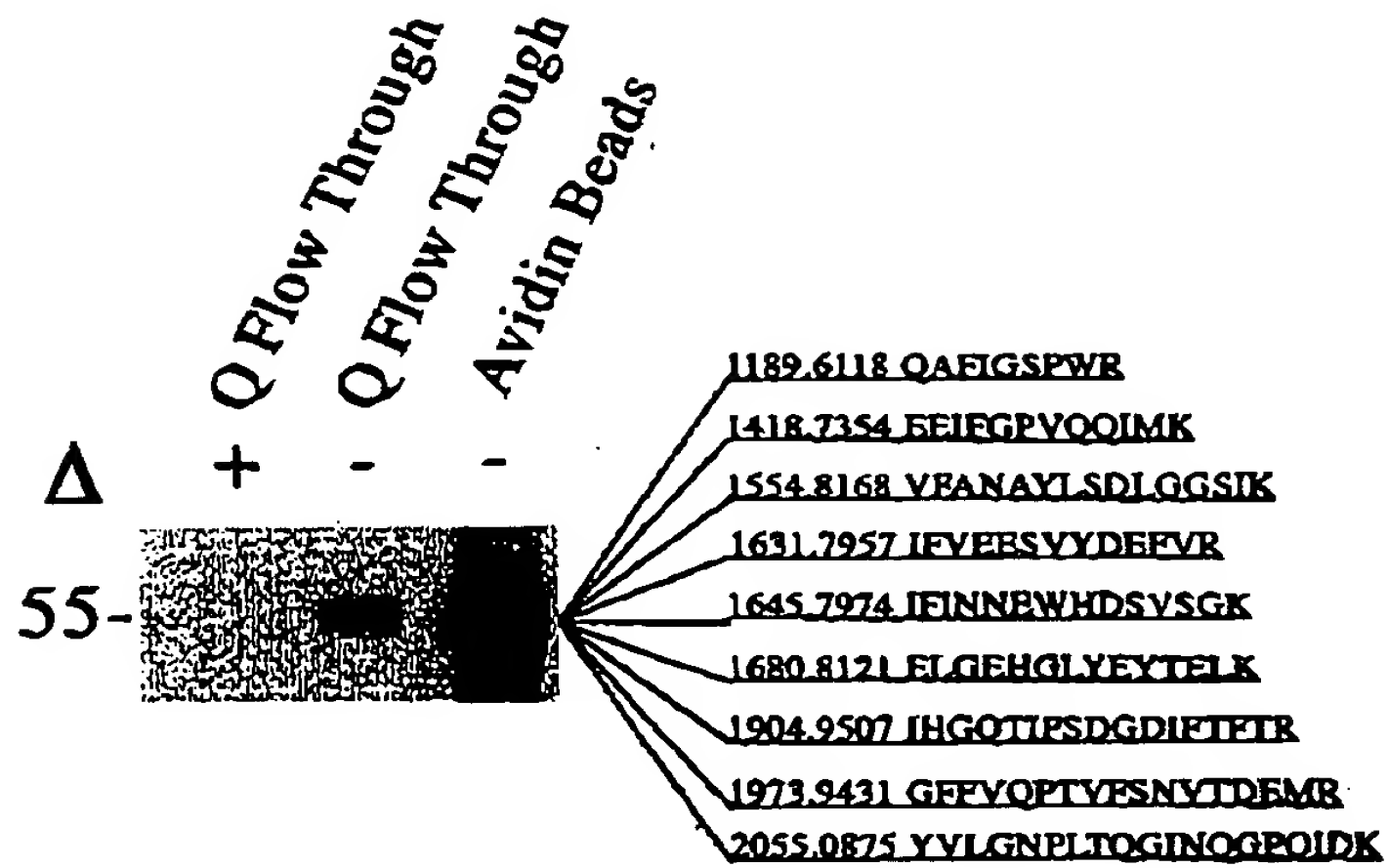
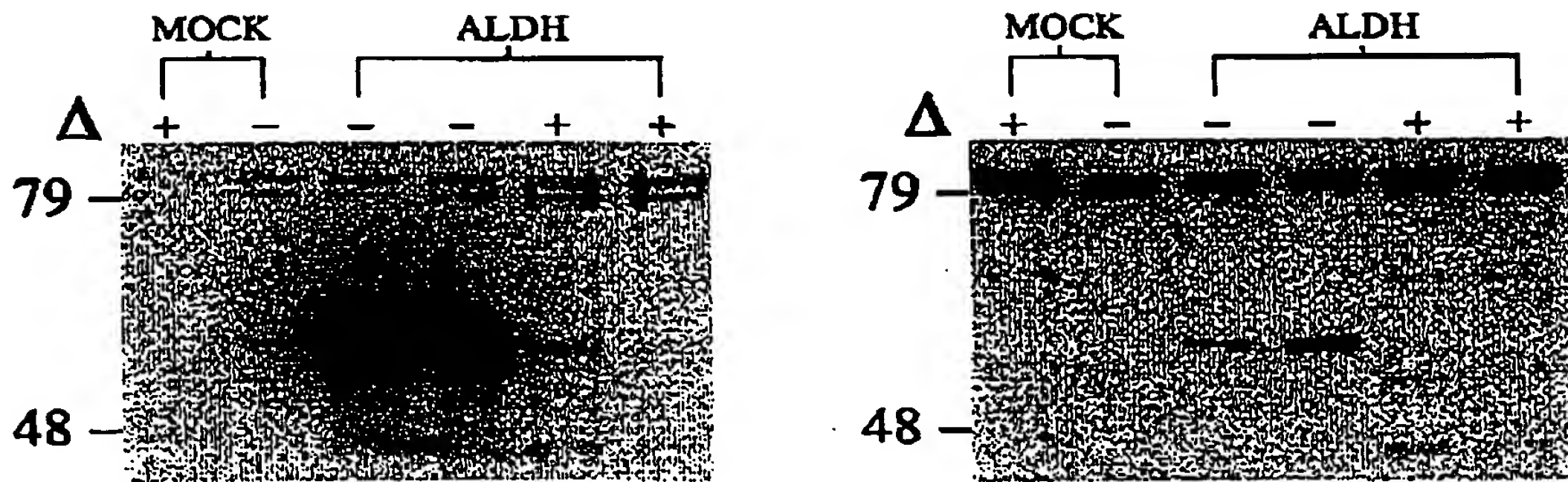


FIGURE 13

A



B



C

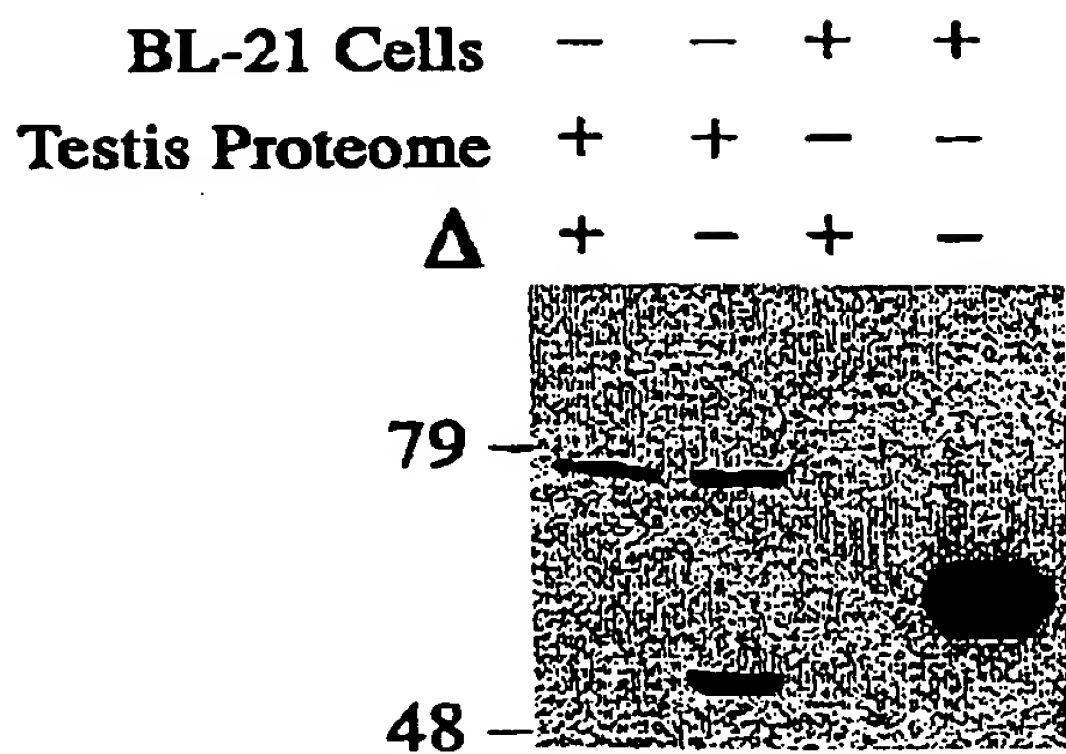
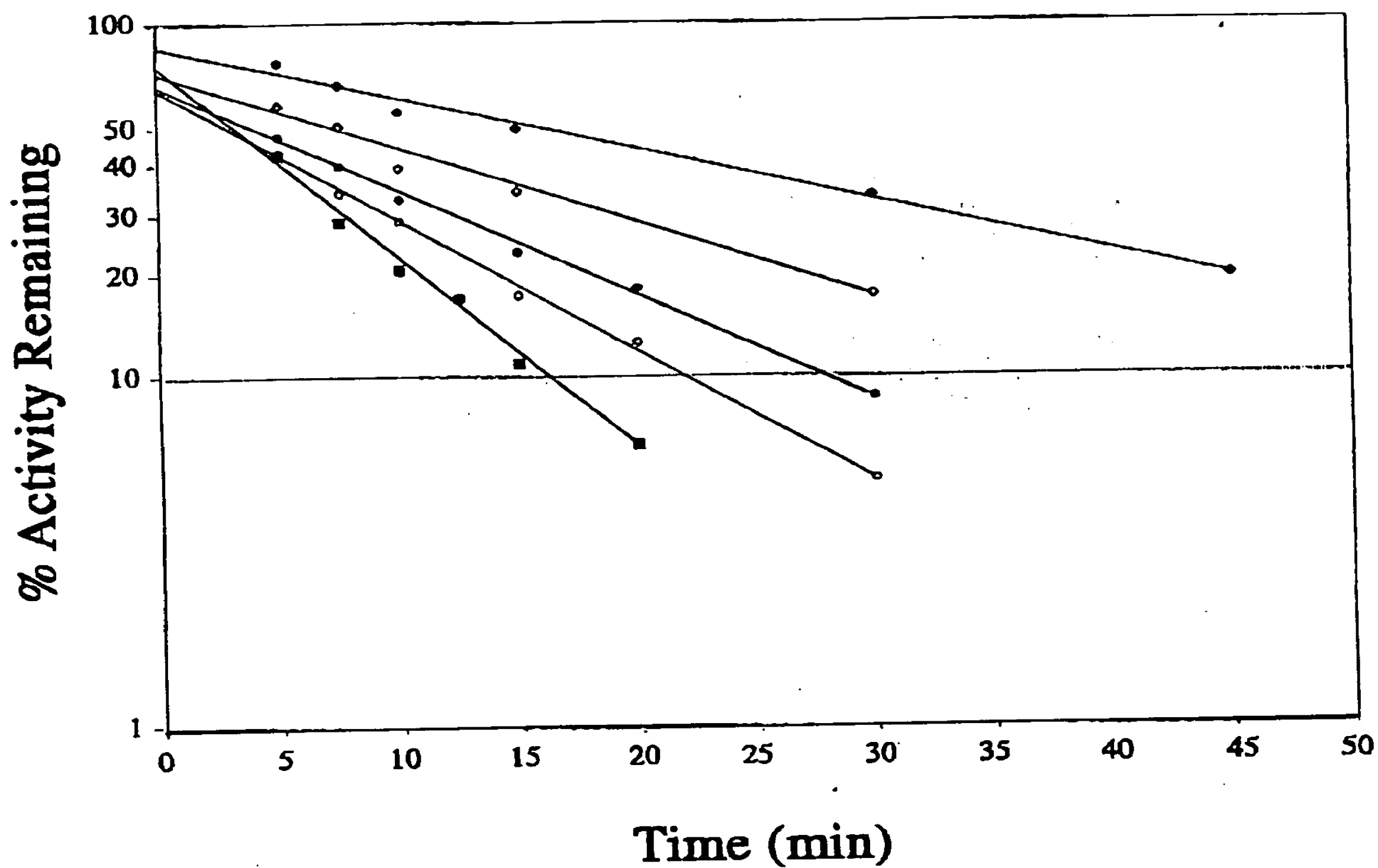


FIGURE 14

A



B

Competitor #	-	-	15	17	16	15	17	16
[Competitor (μ M)]	0	0	5	5	5	50	50	50
Δ	+	-	-	-	-	-	-	-

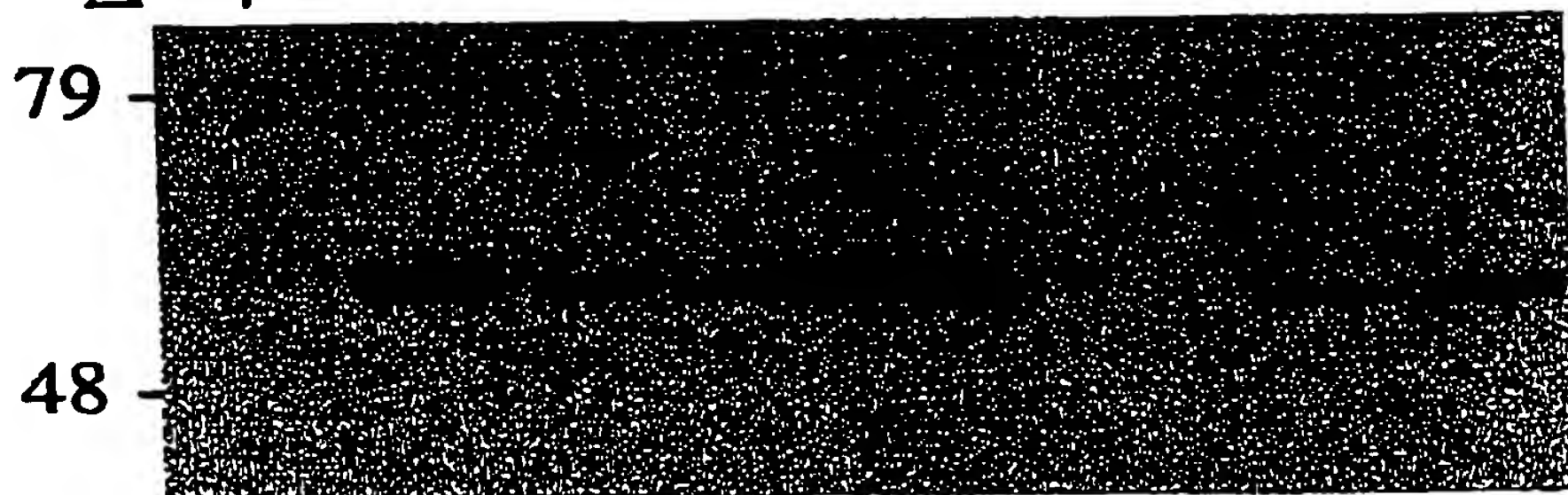


FIGURE 15

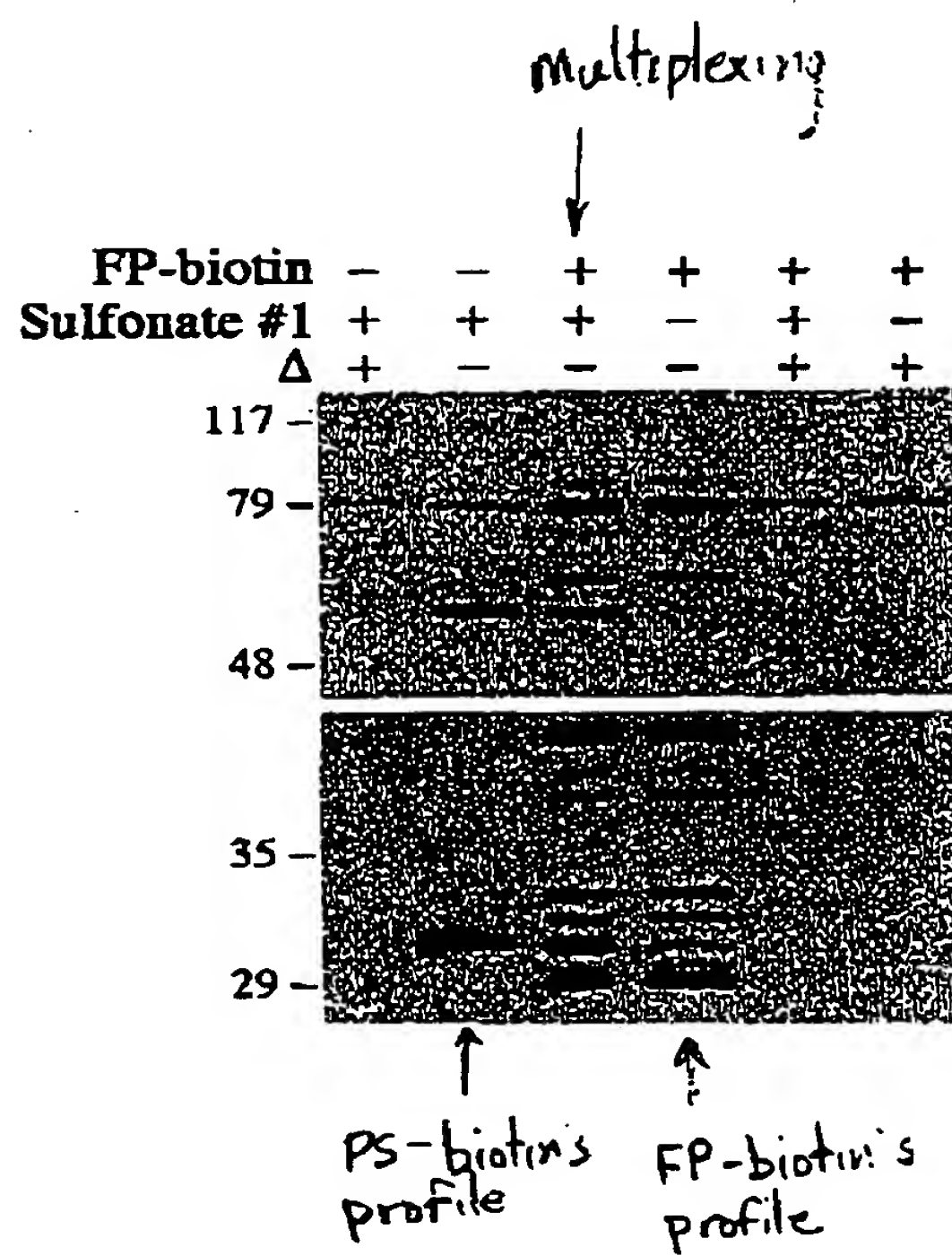


FIGURE 16

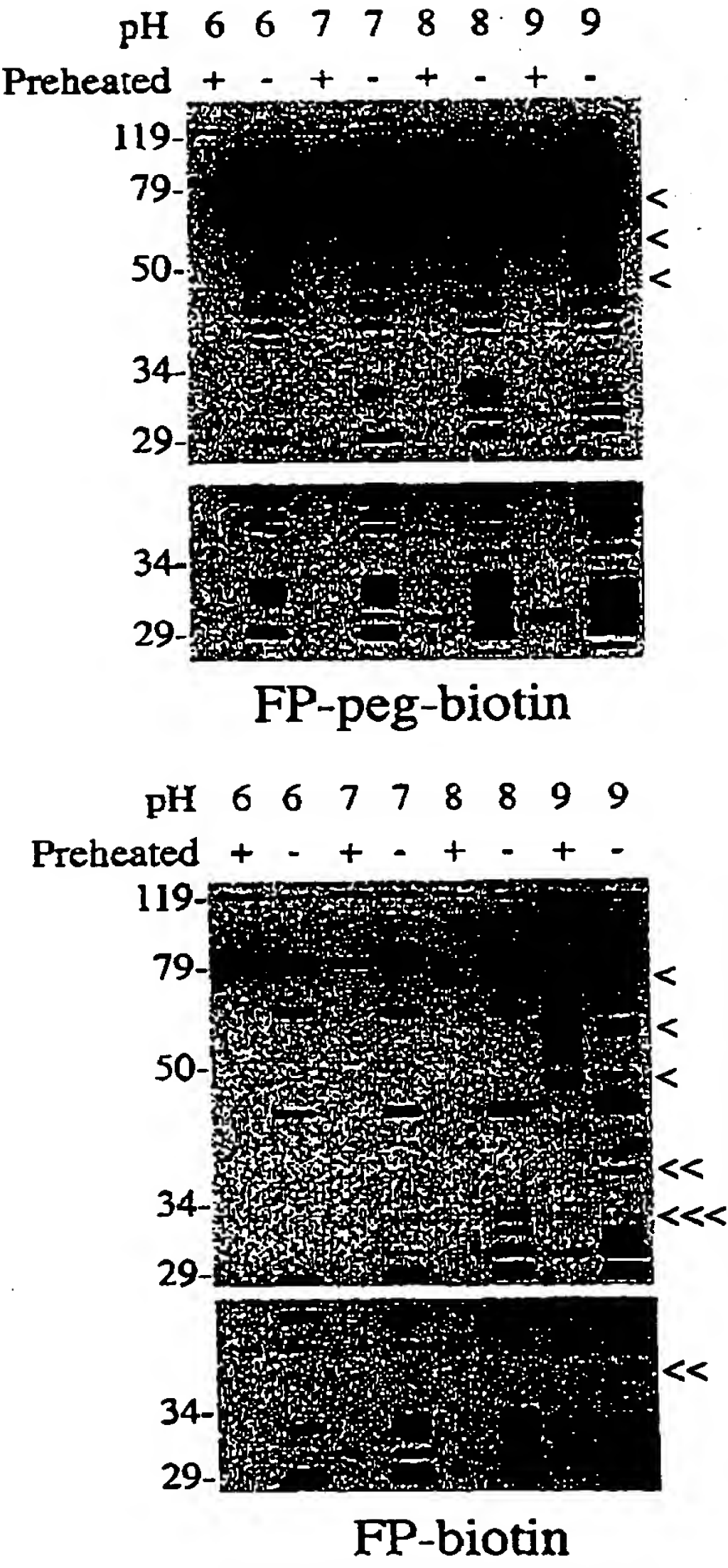


FIGURE 17

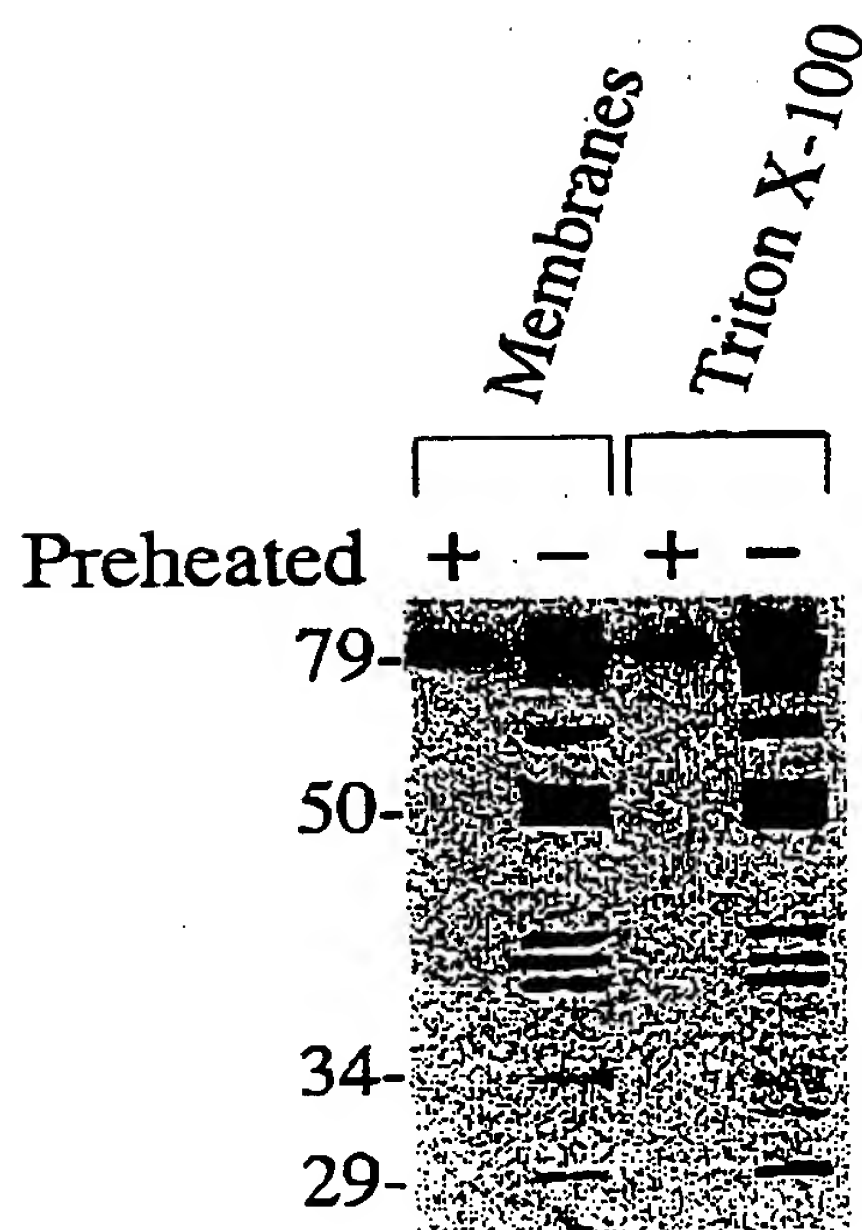


FIGURE 18

FP-peg-biotin	+	+	+	+	+	+	-	-	-
FP-biotin	-	-	-	-	-	-	+	+	+
OTFMK	0	0	200	50	5	1	0	200	50
Δ	+	-	-	-	-	-	-	-	-

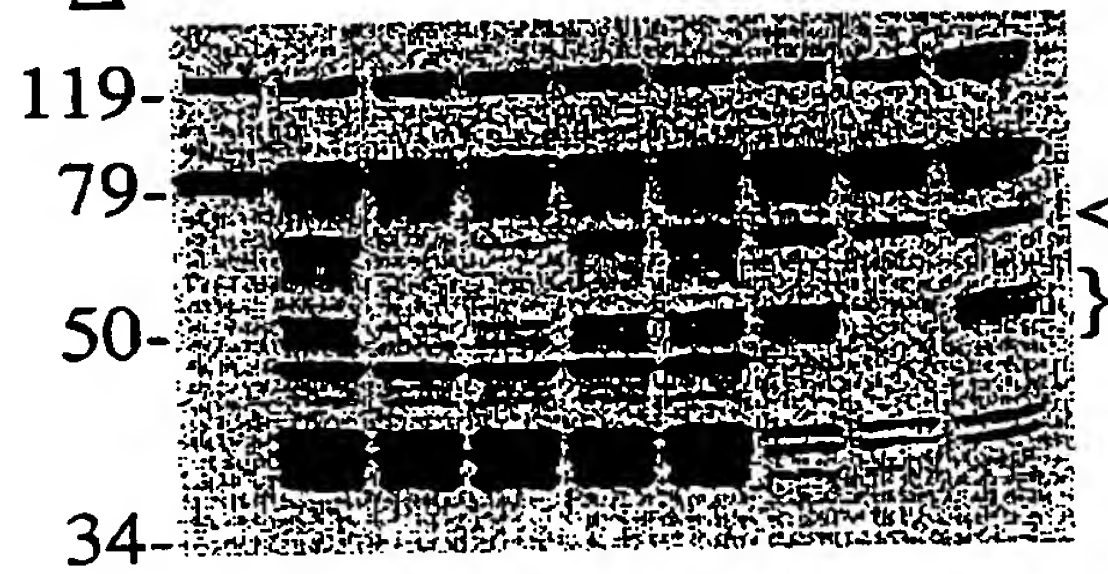


FIGURE 19

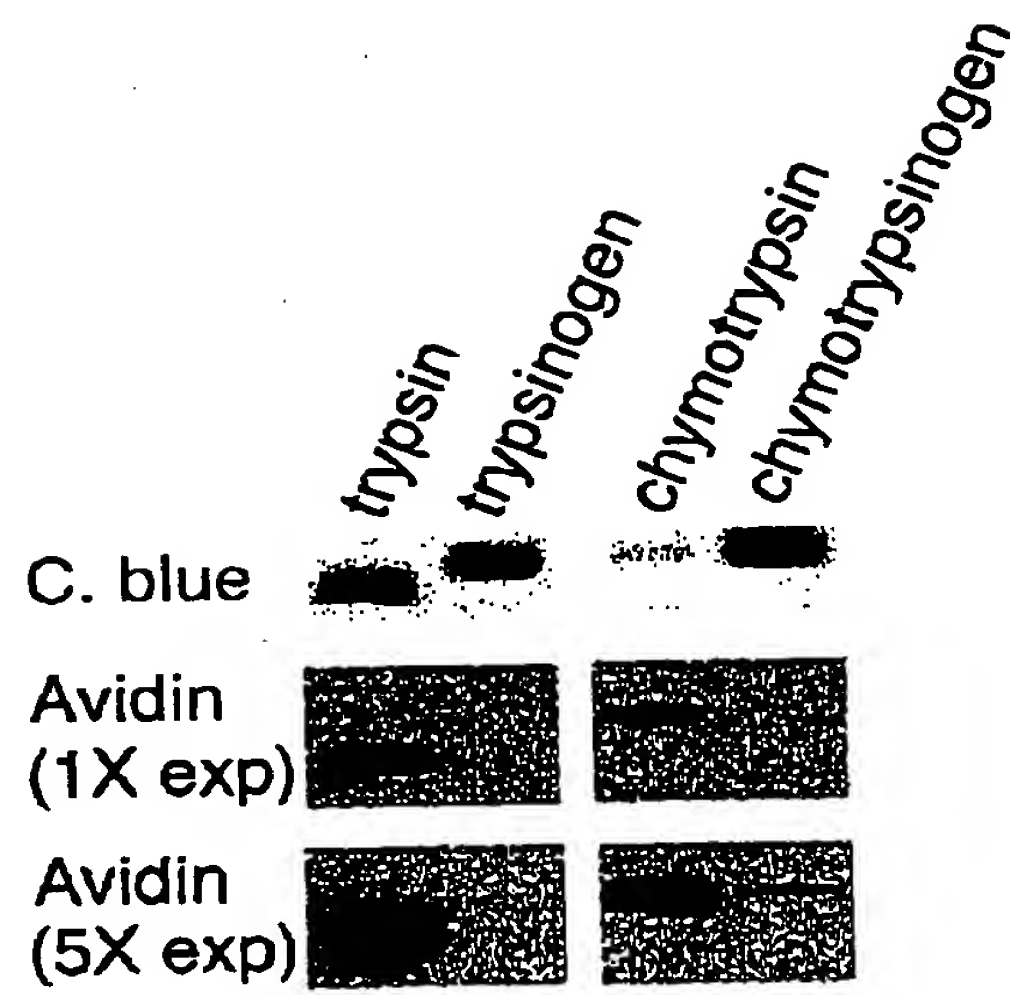
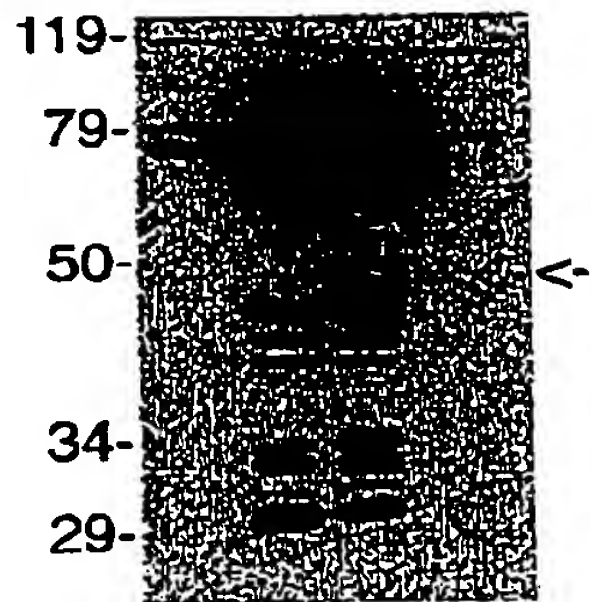


FIGURE 20

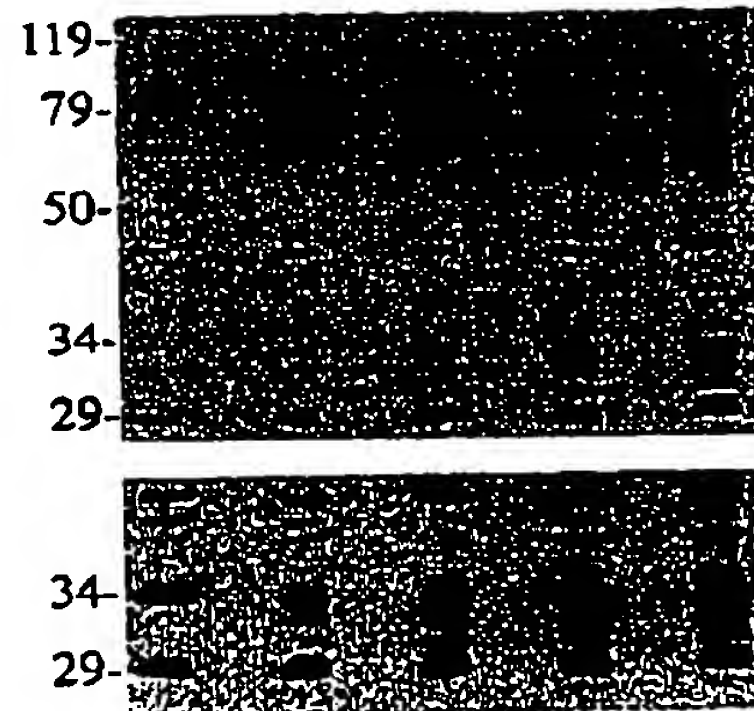
A

FP-peg-biotin	-	-	+	+
FP-biotin	+	+	-	-
Preheated	+	-	-	+



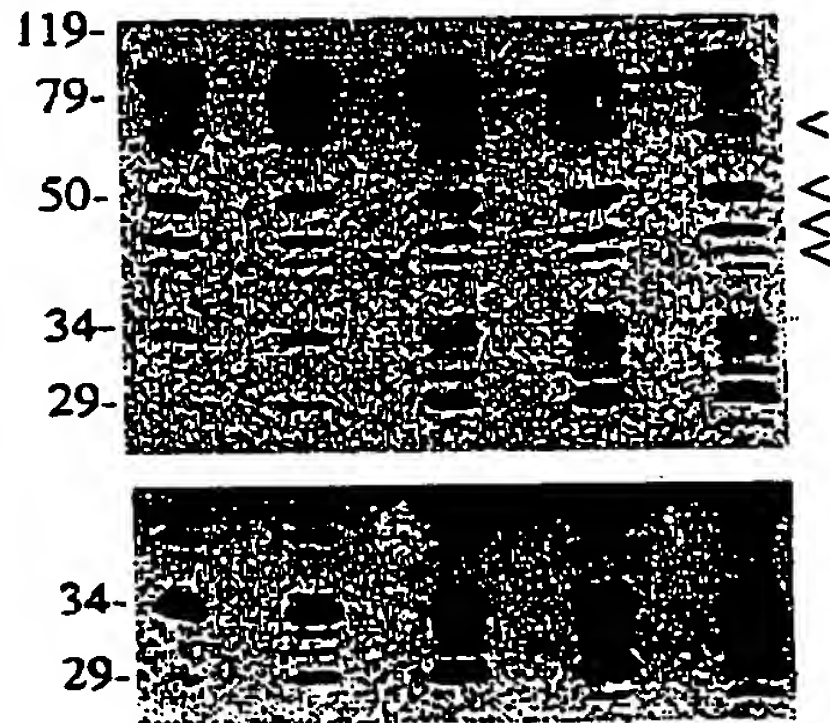
B

FP-biotin (μ M)	0.5	1	1	2	2	4	4	8	8
Preheated	-	+	-	+	-	+	-	+	-



C

FP-peg-biotin (μ M)	0.5	1	1	2	2	4	4	8	8
Preheated	-	+	-	+	-	+	-	+	-



D

FP-peg-biotin (μ M)	1	2	8
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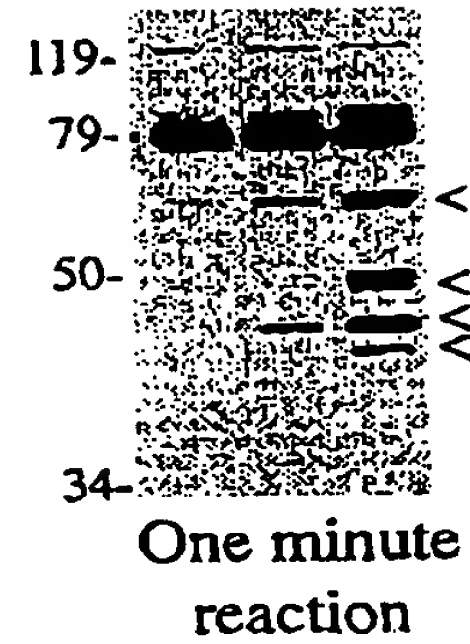


FIGURE 21

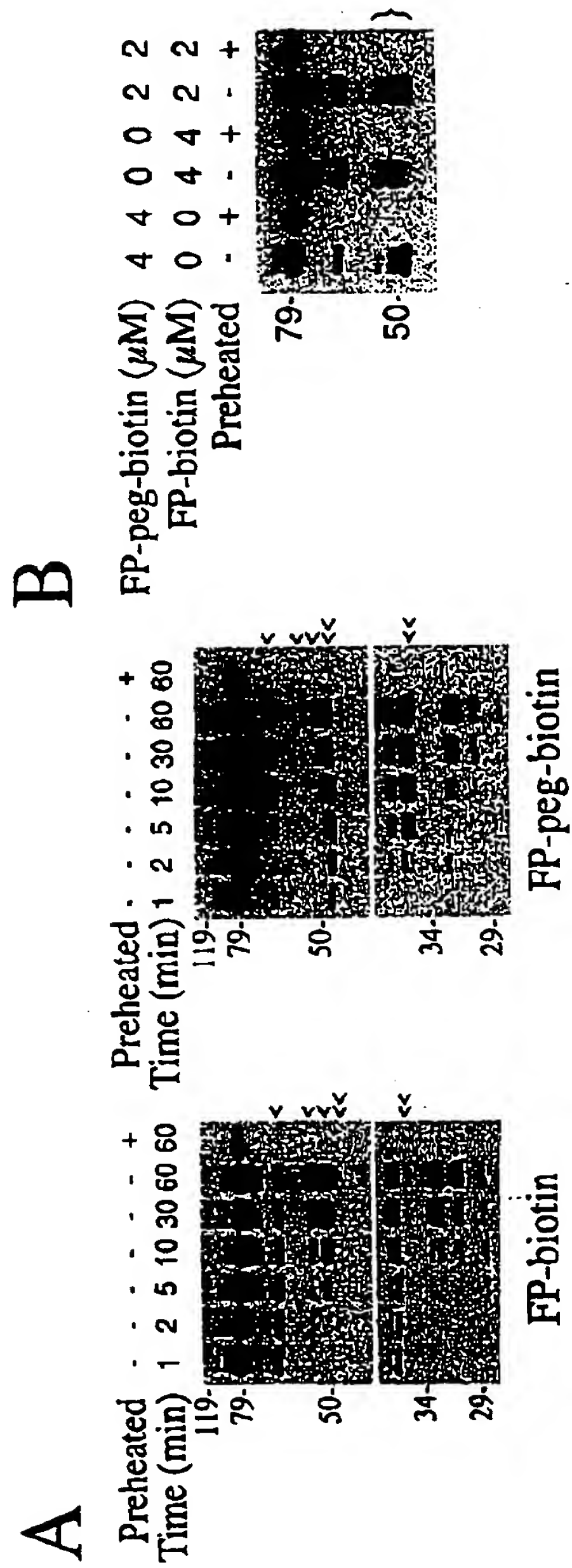


FIGURE 22

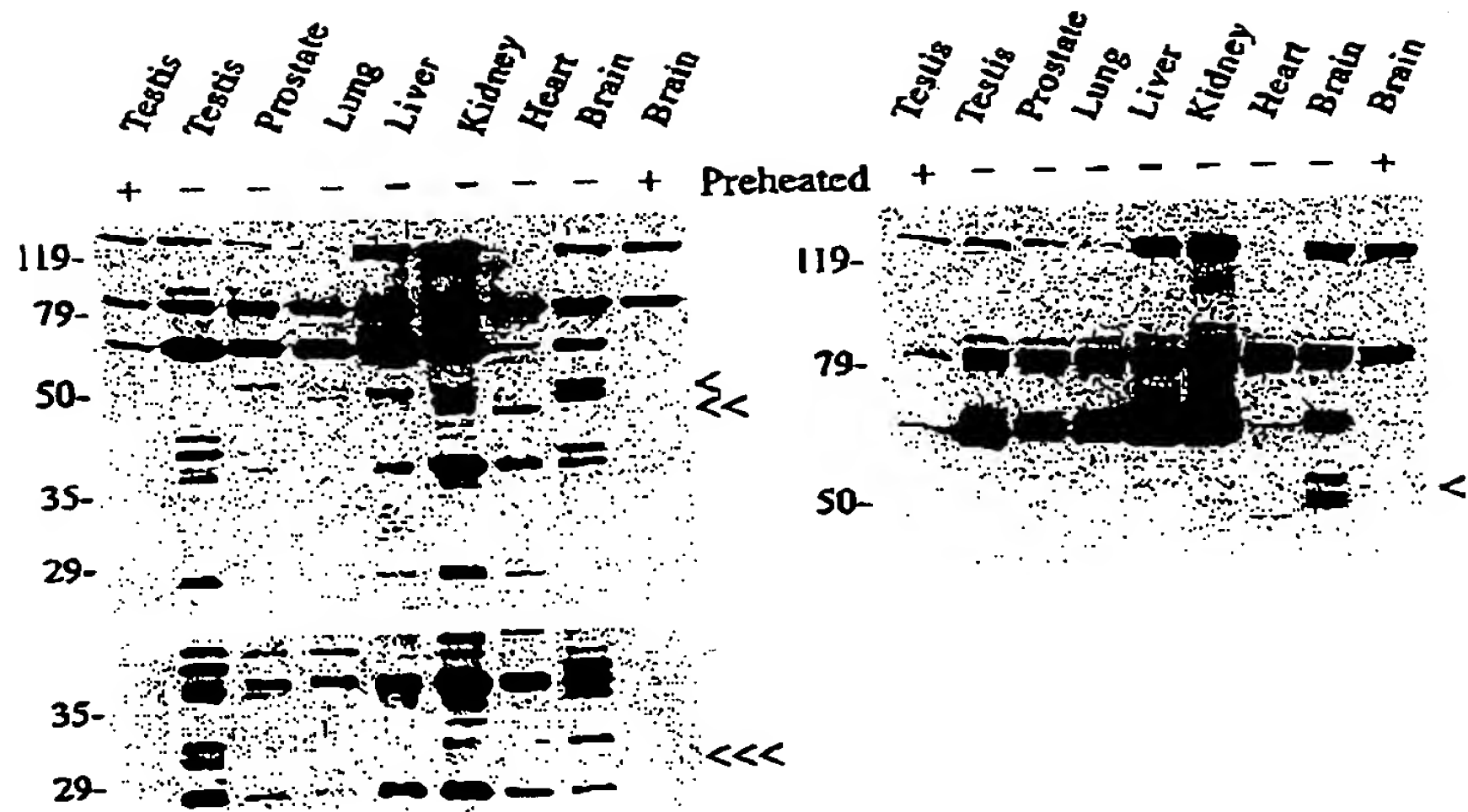


FIGURE 23

